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Consumer organizations and networks

Potential key actors to raise the awareness of antibiotic resistance

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Abstract

Consumer organizations and networks - Potential key actors to raise the awareness of antibiotic resistance

Ann-Sofie Magnusson

Antibiotics have saved lives and helped us to control infectious diseases, but the emergence of antibiotic resistant bacteria is now jeopardizing our health and possibility to treat bacterial infections, and signs in the last century suggest a problematic future. The consequences of misuse and overuse of antibiotics have not been expressed properly alongside the antibiotic development, postponing possible counter-actions.

The main aim of this project, initiated by ReAct – Action on Antibiotic Resistance, was to map and list organizations, focusing on consumer organizations and networks, health networks and Non-Governmental Organizations, which are working in areas where antibiotic resistance is, or could be, a relevant issue. The purpose was also to examine what the organizations believe to be the main factors promoting resistance and their previous and current engagements concerning antibiotic related questions. A questionnaire was sent out to 250 consumer organizations and networks by e-mail, in order to establish the interest in participating in international counter-actions or in other activities that will increase the awareness of antibiotic resistance. The response rate was 22%, and there is no doubt that there is a great interest in the subject and a willingness of changing the situation as 92.6% of the organizations were interested in working with questions related to antibiotics in the future.

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Sammanfattning

Sedan penicillinet upptäcktes har vi förlitat oss till att bota infektioner med antibiotika. Otroliga mängder liv har kunnat räddas tack vare dessa mediciner och skillnaden mellan livet före och efter penicillinets genombrott är enorm. Vårt användande har ökat likaså vårt beroende, men vi har förlorat respekten för dessa preparat genom att använda dem på fel sätt eller när det inte behövs. Antibiotikaresistens är idag ett av de största hoten mot vår hälsa och är ett stort problem för sjukvården. Bakteriella infektioner blir alltmer svårbehandlade på grund av multiresistenta bakteriestammar och behovet av åtgärder är stort. Aktioner som kan påverka den rådande situationen som präglas av för hög tillgänglighet och överanvändning av antibiotika är nödvändiga.

Så kallad ”över-disk-försäljning” är ett stort internationellt problem viket leder till överanvändning, felanvändning, självmedicinering etc. Detta är en av huvudfaktorerna som bidrar till den snabba resistensutvecklingen. Läkare som skriver ut recept på antibiotika när det inte är nödvändigt, t.ex. vid virusinfektioner, eller som inte ens identifierar orsaken till infektionen leder också till ökad resistens, likaså felaktig användning inom boskapshantering och livsmedelsproduktion, bristande hygien på sjukhus samt avsaknad på nya preparat.

Initiativ för att förhindra denna utveckling involverar flera stora organisationer, och i flera länder har också lagstiftning och kontroller införts för att få bukt på problemen. Antibiotikaresistens är dock ett gränslöst problem och den snabba globaliseringen medför att åtgärder måste göras på internationell nivå för att de ska ha verkan. Konsumentorganisationer har en stor möjlighet att påverka eftersom de har makten att nå den största beslutsfattande gruppen när det gäller användandet av dessa preparat; nämligen oss konsumenter. Samarbete mellan internationella organisationer, nätverk och NGO:s innehar stor kapacitet vilket ligger till grund för denna undersökning. Projektet initierades av ReAct – Action on Antibiotic Resistance, en internationell organisation som arbetar med att övertyga och upplysa olika samhällsgrupper om att antibiotikaresistans är ett reellt problem och att åtgärder måste genomföras för att kunna behandla bakteriella infektioner lika effektivt som idag. Projektets mål var att hitta organisationer intresserade av att samarbeta med ReAct inom detta område.

250 internationella organisationer, nätverk och NGO:s kontaktades och inbjöds till att delta i studien med syftet att kartlägga organisationer intresserade av att arbeta med antibiotikarelaterade frågor i framtiden samt att undersöka intresset av att delta i gemensamma aktioner. Svarsfrekvensen blev 22 % och alla världsdelar är representerade i undersökningen. Resultatet visar att det onekligen finns ett stort intresse för att arbeta med frågor relaterade till antibiotika och att samarbeta för att öka medvetenhet och sprida information. Däremot framgår det att arbetet med denna typ av frågor har minskat under det senaste året (2006) vilket är oroväckande eftersom problemet i allra högsta grad kvarstår.

Att öka medvetenheten hos konsumenter är ett möjligt sätt att angripa problemet på en nivå som kan leda till förändring. Genom att utbilda och informera konsumenterna om detta problem samt att upplysa om konsekvenserna av ett oförändrat beteende, finns möjligheten att påverka den allvarliga situation som vi själva har åstadkommit.

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Abbreviations

DNA	Deoxyribonucleic acid
MDR-strain	Multidrug resistant strain
mRNA	Messenger ribonucleic acid
MRSA	Methicillin-resistant *Staphylococcus aureus*
NGO	Non-Governmental Organization
PHM	People's Health Movement
ReAct	Action on Antibiotic Resistance
tRNA	Transfer ribonucleic acid

Glossary

Amino acid	One of the 20 building blocks of protein
Anticodon	A sequence of three nucleotides in tRNA that binds to a corresponding codon in mRNA
Bactericidal	An agent that kills bacteria
Bacteriophage	A virus that infects bacteria, also called a phage
Bacteriostatic	Capable of inhibiting reproduction of bacteria
Codon	A set of three adjoined nucleotides that code for an amino acid or a termination signal
Collagen	A protein that is the main support of skin, bone, connective tissue
Comparative genomics	The study of human genetics by comparisons with model organisms
Efflux	An outward flow
Enzyme	A protein that accelerates the rate of chemical reactions
Folic acid	One of the vitamins that is a key factor in the synthesis of nucleic acid
Functional genomics	The function of each gene in the genome
Genome	The complete set of genetic information of an organism including DNA and RNA

Gram-negative/ gram-positive bacteria	Gram-positive bacteria are stained dark blue or violet by gram staining, in contrast to gram-negative bacteria, which are not affected by the stain. The stain is caused by a high amount of peptidoglycan in the cell wall, which typically lacks the secondary membrane and lipopolysaccharide layer found in Gram-negative bacteria
Gyrase	Gyrase is an enzyme active in the DNA replication process
Horizontal gene transfer	Transmission of DNA between species
Hydrolysis	Decomposition of a chemical compound by reaction with water
Ligand	Any molecule that binds to another
Microorganism	An organism of microscopic or sub microscopic size
Pathogen	An organism that causes disease in another organism
Peptide	Two or more amino acids chained together by a bond called a peptide bond
Peptidoglycan	Large polymer that provides much of the strength and rigidity of bacterial cell walls
Plasmid	A circular, double-stranded unit of DNA that replicates within a cell independently of the chromosomal DNA
Proteomics	The study of proteins and their functions
PubMed	Online database of scientific literature
Ribosome	Cellular organelle that is the site of protein synthesis
Transpeptidase	A transpeptidase is a bacterial enzyme which cross-links the peptidoglycan chains to form rigid cell walls
Transposon	A mobile genetic element that can move from one location in the gene and reinsert at another site

1 Introduction

1.1 The growing problem of antibiotic resistance

It is not even a century ago since the miracle of penicillin was discovered. The year of discovery was 1928, and in the early 1940's, antibiotics started to spread over the world war battlefields, revolutionizing medical care[1]. Today, in 2007, the respect for antibiotics has changed dramatically. Antibiotic resistance is a fast growing threat to our future health by jeopardizing our possibility to treat bacterial infections. Although resistance seems to be a relatively new subject of discussion, it is far from a new occurrence. Just a few years after the new medicine was taken into use, Alexander Fleming announced his apprehension concerning the use of the preparation, during his Nobel Prize acceptance speech in 1945[2]:

> *"There may be a danger […] in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. […] Moral: If you use penicillin, use enough."*

The decades after the discovery of penicillin, the discovery and production of new antibiotics and antibiotic classes was high, always ensuring an alternative and effective treatment, but in reality only concealing the growing resistance[3]. At present, when the production and the discovery of new antibiotics do not even resemble earlier years, we are forced to face the problem. Many of our most powerful antibiotics are now becoming ineffective causing difficulties in treatments of diseases like tuberculosis, cholera, diarrhoea and pneumonia. These are examples of diseases that already kill more than ten million people each year[4]. Still we rely and depend on antibiotics for cure, and a future without antibiotics is, to put it mildly, uncertain. We are not prepared for a life without antibiotics and therefore it is clear that something has to be done about the growing resistance. Ignoring the problem with misuse and overuse will only aggravate the situation and complicate treatments of bacterial infections further, as bacteria have been forced to protect themselves. Instead of trying to live in symbiosis with bacteria, we have lately been pushing the balance, and antibiotics have created a paradox: The more redundant and carelessly used antibiotic treatments we expose ourselves to, an increasing rate of resistance will be seen, resulting in poorer effectiveness of the antibiotics.

1 Wilson, D.,(1976). p. 204.
2 Nobelprize.org (2006). (2006-12-14).
3 Shalala, D. E., (1998).
4 World Health Organization (2006). (2006-09-05).

1.2 Networking as a way to spread awareness

The problematic and dangerous consequences of misuse and overuse have not been expressed properly alongside the antibiotic development, postponing possible counter-actions. Today, when we live in a society characterized by information distribution, with several means to educate people, it seems like it should not be an overwhelming task. However, in reality the process of educating the public and raising the awareness to the point where slow moving systems and traditions are transformed and revolutionized, is a time-consuming and demanding mission. One way, proven to make this kind of change possible, is to form networks*. By using networking as a model to raise awareness, people from all over the world are brought together and are given the opportunity to exchange ideas and express opinions and thoughts to others. As the problem of antibiotic resistance is global, an international counter-action is essential to prevent the problem of resistance from getting out of proportion, and becoming an unmanageable problem to tackle.

In the last years, several initiatives have been proposed aiming to decrease the resistance, and the engagement concerning this matter has increased. Still, results showing decreased resistance on a global perspective are hard to find, and new ideas and efforts are needed. ReAct, Action on Antibiotic Resistance, is a coalition with collaborators on all continents, working toward the goal of keeping antibiotics effective. The coalition was formed in 2004 as a result of an international meeting at the Dag Hammarskjöld Centre in Uppsala**, where the issue of antibiotic resistance and the knowledge distribution of resistance were discussed. ReAct was initiated with the purpose of convincing policy-makers, doctors, scientific and research organizations as well as civil society that action must be taken to be able to tackle the threat of antibiotic resistance. Further, the coalition also wishes to inform, involve and mobilize communities and to protect their right to safe and effective treatment of bacterial infections.[5] ReAct recognizes the importance of engaging people and organizations on different levels in society in order to attack the problem effectively. A possible group, of great power to demand a change in the systems of distribution and use of antibiotics, is the consumers. International consumer organizations and networks are strong in both quantity and engagement. Increasing the awareness of antibiotic resistance, and its consequences, among the public could be a way to achieve a change. This project was initiated by ReAct as an attempt to find organizations and networks with an interest in questions related to antibiotic resistance and a willingness of participating in joint actions.

* International Campaign to Ban Landmines (ICBL) was awarded the Nobel Peace Prize in 1997 for their work of banning and clearing anti-personnel mines through international networking.

** The meeting was organized by the Dag Hammarskjöld Foundation, Division of International Health (IHCAR) of Karolinska Institutet and STRAMA (the Swedish Strategic Program for The Rational use of Antimicrobial Agents).

5 ReAct (2006). (2006-10-01).

1.3 Main aim

The main aim of this project is to map and list organizations, focusing on consumer organizations and networks, health networks and other NGOs (Non-Governmental Organizations), which are working in areas where antibiotic resistance is, or could be, a relevant issue.

1.3.1 Specific objectives

- To examine if the organizations and networks have worked with questions related to antibiotic resistance previously.
- If they are currently engaged in activities trying to slow down the emerging antibiotic resistance, and if so in what ways they are contributing to this process.
- If there is interest in working with questions related to antibiotic resistance in the future, and if so what kinds of projects they are willing to participate in.

Counter-actions in the form of networking and organizational engagement may represent ways to spread knowledge and increase the understanding of the problem. Aiming to overview the situation on a global scale from the consumer organizations' and networks' point of view, the interest of antibiotic resistance, the on-going efforts aiming to improve the situation, and the opinions of international networks and organizations on awareness raising, is examined. The consumers, which this study focuses on, may constitute an important part when trying to slow down the growing resistance and to change the prevailing situation characterized by misuse and overuse of antibiotics. This study aims to localize these groups on an international level as a step to assemble a joint action against the growing antibiotic resistance – one of the most serious threats to our health today.

2 Background

2.1 Antibiotic resistance

2.1.1 The first antibiotic

Throughout history, humans have treated aches and pains with various remedies, sometimes more creative than effective. Beer soup with ground snake skins and turtle shells, or frog bile and sour milk[6] may not belong to our common treatments today, but remembering that antibiotics have just been accessible for about 60 years, and that bacterial infections date back to the beginning of time, the need for a cure has spurred inventiveness. In the middle of the 19th century, the French microbiologist and chemist Louis Pasteur observed that some microorganisms could destroy other microorganisms, and this possibility of using harmless microbes to fight pathogens is noted to be the first underlying principle of antibiotics[7]. In 1928, the Scottish bacteriologist, Alexander Fleming, left a culture of *Staphylococci* bacteria uncovered in his laboratory at St Mary's Hospital in London. A few weeks later he noticed that mould had grown on the Petri dish, secreting a substance that prevented the *Staphylococci* bacteria to grow. The mould *Penicillium notatum* was identified, and Fleming named the substance penicillin. He later tried to purify penicillin, but did not succeed. In 1940 pathologist Howard W. Florey and chemist Ernst B. Chain, successfully used a small sample of Fleming's mould to produce a sample of penicillin a million times more powerful than the original filtrate.[8] In 1945, Fleming, Florey and Chain were awarded the Nobel Prize in Medicine[9].

2.1.2 The situation today

Antibiotics have saved lives and helped us to control infectious diseases, but the emergence of resistant bacteria is now jeopardizing our health and signs in the last century suggest a problematic future. The first drug-resistant strain, sulfonamide-resistant *Streptococcus pyogenes*, was detected in the 1930's in military hospitals, and soon after the introduction of penicillin in the 1940's, penicillin-resistant *Staphylococcus aureus* appeared in civilian London hospitals. Similarly, streptomycin-resistant *Mycobacterium tuberculosis* was detected in the community soon after it had been taken into use. In the late 1950's to early 1960's, the first resistance to multiple drugs was identified among *Escherichia coli*, *Shigella* and *Salmonella*. Strains resistant to multiple drugs caused great problems and cost many lives, especially in developing countries. In industrialized countries, antibiotic resistance was commonly seen as a small problem in far-away places, but when organisms causing respiratory and genitourinary diseases, started to develop resistance in industrialized parts of the world in the 1970's, the attitude started to change. Since the 1980's, multi-drug resistant (MDR) tuberculosis has emerged and the treatment of this disease, in some cases, involves six to seven different drugs due to the MDR strains.[10] Today, the bacterial infections that cause most human diseases; respiratory tract infections, diarrhoeal

6 Hoel, D., Williams, D. N., (1997).
7 Wilson, D., (1976), p. 19-28.
8 Nobelprize.org (2006). (2006-10-02).
9 Ibid.
10 Levy, S. B., Marshall, B., (2004).

diseases, meningitis, sexually transmitted infections and hospital-acquired infections, represent the infections in which resistance is most apparent. Examples of resistance include penicillin-resistant *Streptococcus pneumoniae,* vancomycin-resistant *Enterococcus,* methicillin-resistant *Staphylococcus aureus,* multi-resistant *Salmonella*, and multi-resistant *Mycobacterium tuberculosis*. Tuberculosis re-emerged during the 1990's as one of the leading causes of mortality worldwide, with a particularly severe situation in developing countries. Poor treatment of this disease is one of the main promoters for the emergence of multi-drug resistant strains[11]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing problem in many hospitals and up to 60% of hospital-acquired infections, in industrialized countries, are due to drug-resistant microbes as MRSA. These kinds of infections are now beginning to spread in the general community.[12] The problem is escalating world wide, and for example about half of the *Staphylococcus aureus* strains in the United States and in the United Kingdom are methicillin-resistant, and associated with very difficult treatments.[13]

The rising numbers of bacterial strains with resistance genes suggest that the future of bacterial treatments may not include antibiotics. Resistance in *Escherichia coli* to traditional antibiotics is now common in Europe, with only Finland and Sweden reporting resistance rates of less than 30%. A study surveying 25 countries resulted in resistance rates from 25% to 64%.[14] Statistics presented by The Swedish Institute for Infectious Disease Control (SMI) show the trend of the growing resistance in Sweden, one of the countries least affected by resistance, see Figure 1. The development of resistant *Streptococcus pneumoniae* in Sweden is similar to the development of resistance in *Escherichia coli* and is shown in Figure 2.

The emergence of antibiotic resistance is most evident and has become a public health issue[15]. Infections caused by resistant bacteria can result in prolonged illness and greater risk of death. Treatment failures due to the resistant strains can also lead to longer periods of infectivity, which increase the numbers of infected people moving around in the community. This means that the general population is exposed to a greater risk of contracting a resistant strain of infection. Some diseases are developing resistance for almost all available antibiotics[16], and without a cure, these diseases pose a great challenge to our healthcare.

11 European Commision (2007). (2007-02-13).
12 Ibid.
13 World Health Organization (2007). (2007-02-01).
14 Sheldon, T., (2004).
15 Bud, R., (2007).
16 World Health Organization (2007). (2007-02-05).

Figure 1. Escherichia coli; antibiotic resistance. Sweden 1996-2006.[17]

The increasing trend of antibiotic resistance in E.coli in Sweden between 1996-2006. Statistics from the Swedish Institute for Infectious Disease Control

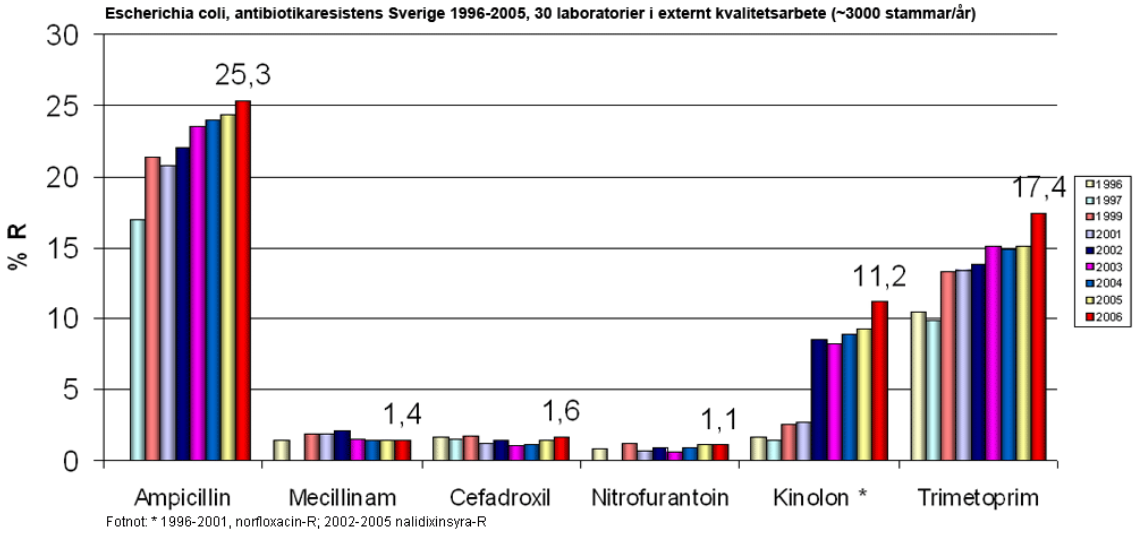
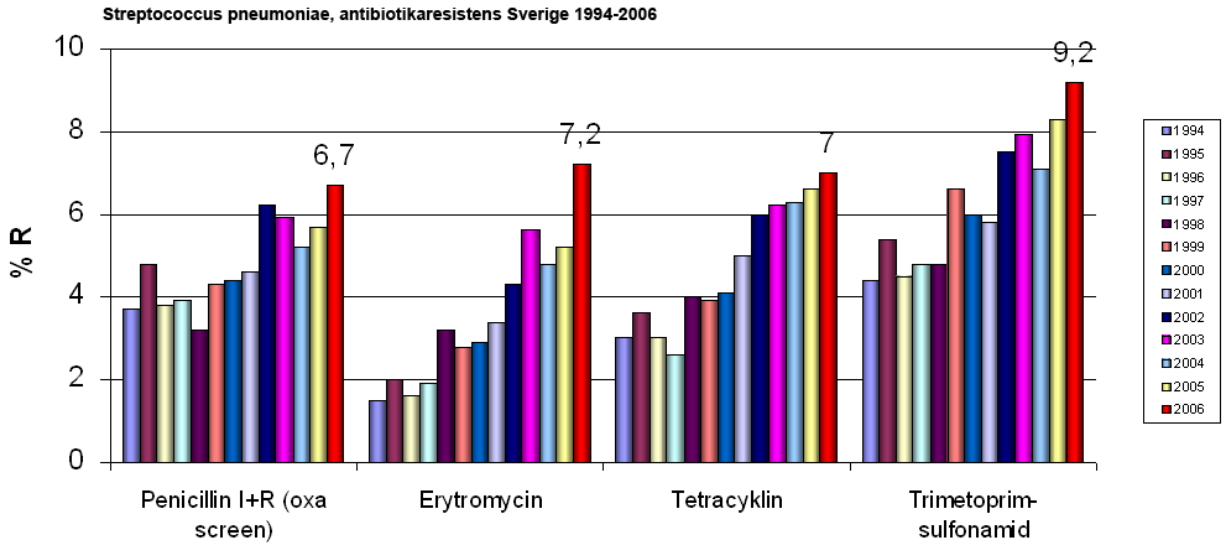


Figure 2. Streptococcus pneumoniae; antibiotic resistance in Sweden 1994-2006.[18]

The development of antibiotic resistance in Streptococcus pneumoniae in Sweden between 1994-2006.



17 Smittskyddsinstitutet (2007). (2007-03-06).
18 Ibid.

2.1.3 Research and possible new targets

2.1.3.1 Background to antibiotics and resistance mechanisms

Antibiotics (from the Greek anti = against, bios = life) are defined in Encyclopaedia Britannica as chemical substances produced by a living organism, generally a microorganism, harmful to other microorganisms[19]. Some substances are however synthetic compounds (not produced by microorganisms), but are also killing or inhibiting the growth of microbes[20]. There are many ways in which antibiotics can be classified. Chemical structure, mechanism of action, route of administration (injectable/oral) and type of activity (bactericidal/bacteriostatic) are among others, ways to divide different antibiotics into classes.[21,22,23] Figure 3 summarizes some of the most common antibiotics, according to mechanism of action to facilitate the understanding of this chapter, where the classes are used in the descriptions of the action of the antibiotics, and in the examples of resistance mechanisms.

Antibiotic resistance is a natural phenomenon due to natural selection. Environmental changes, natural or man-made, have been challenging bacteria to evolve, and "the survival of the fittest" is the simple expression that explains the development. All organisms are participants of the constantly on-going process of evolution. The danger does not lie in the natural evolution, but in the accelerated and forced increase of resistance caused by positively selecting resistace genes in the bacterial population. Resistant bacteria may eventually outnumber the non-resistant, leaving antibiotic treatments powerless.

Bacteria can become resistant to antibiotics either by spontaneous mutations or by horizontal gene transfer. Mutational resistance arises after random mutations in a bacterial population, resulting in domination of the altered and resistant bacteria. Horizontal gene transfer occurs directly between bacteria, mediated by e.g. plasmids. Examples of some mechanisms of resistance are presented below and some are further explained later in this chapter; [24]

- Decreased uptake and/or accumulation of the antibiotic
- Drug target modification
- Hydrolysis of the antibiotic
- Increased efflux
- Modification of the antibiotic
- New antibiotic resistant target
- Plasmid-mediated resistance/amplification and overproduction of target or modification enzymes

For increased understanding of the mechanisms of resistance and the antibiotic actions, Appendix A contains an overview of the bacterial cell and the specific functions of the cell associated with antibiotic targets and resistance.

19 Encyclopedia Britannica (2006). (2006-09-25).
20 Centers for Disease Control and Prevention (2006). (2006-10-02).
21 Samaha-Kfoury, J. N., Araj, G. F., (2003).
22 King, D. E., Malone, R., Lilley, S. H., (2000).
23 Åbom, P. E. (1994), s.316.
24 Normark, B. H., Normark, S., (2002).

Figure 3. Classes and mechanisms of action of antibiotics[25,26,27]

Mechanism of action	**Antibiotic class**		**Examples**
Inhibition of cell wall synthesis	β-Lactam antibiotics	Penicillins	Benzylpenicillin Ampicillin Amoxycillin Cloxacillin Fenoximetyl-penicillin Piperacillin
		Cephalosporins	Cefadroxil Cefazolin Cefuroxime Cefoxitin Cefpodoxime
		Carbapenems	Imipenem Meropenem
		Monobactams	Aztreonam
	Glycopeptides		Vancomycin Teicoplanin
Inhibition of nucleic acid replication	Quinolones		Nalidixic acid Ciprofloxacin Norfloxacin Moxifloxacin
	Rifamycines		Rifampicin Rifabutin
Inhibition of protein synthesis	Aminoglycosides		Gentamicin Tobramycin Netilmicin Amikacin Neomycin
	Macrolides Azalides Lincosamides		Erythromycin Clarithromycin Azithromycin Clindamycin Lincomycin
	Tetracyclines		Lymecycline Metacycline Doxycycline Oxytetracycline
	Oxazolidinones		Linezolid
Inhibition of cell metabolism	Folic acid antagonists		Trimethoprim Sulfonamides

25 Norrby, R., Cars, O., (1997).
26 Hammond, S. M., Lambert, P. A., (1978), p.7ff.
27 Diekema, D. I., Jones, R. N., (2000).

Cell wall synthesis inhibitors – antibiotic action and resistance
Peptidoglycan, a major constituent in the bacterial cell wall, is unique to bacteria and therefore easily targeted[28]. The β-lactam antibiotics are the oldest class of antibiotics used to treat bacterial infections[29], and the penicillin class represents the most widely used antibiotics. β-lactam antibiotics act by inhibiting the bacterial cell wall synthesis, and by forming a complex that blocks the transpeptidase enzyme, the linking activity of the transpeptidase is inhibited.[30,31] They can also attach to the penicillin binding proteins, which normally suppress cell wall hydrolysis, damaging the biosynthesis of peptidoglycan, which results in the inhibition of growth or in cell lysis.[32,33]

A major mechanism of resistance to β-lactam antibiotics is the synthesis of the bacterial enzyme, β-lactamase, which mediates antibiotic hydrolysis[34]. The β-lactamase enzyme cleaves the structural ring of the β-lactam antibiotic, which results in the inactivation of the transpeptidase enzymes that normally catalyzes the peptidoglycan synthesis. In some bacterial species this mechanism has been refined, and the synthesis of β-lactamase is automatically induced in the presence of a β-lactam antibiotic.[35] The mechanism of the β-lactamase is an example of mutational modification. Resistant bacteria keep the same targets as antibiotic sensitive bacteria, but prevent the antibiotic from reaching it.[36]

Nucleic acid replication inhibitors – antibiotic action and resistance
DNA (deoxyribonucleic acid) acts as template molecules in both replication and transcription in the bacterial cell. Antibiotics can damage these functions by binding to the DNA molecule, either forming a complex, which inhibits the function of the DNA, or the antibiotics can attack the DNA more directly by breaking the strands or removing nucleotides.[37] The most important mechanism is however the formation of complexes. This is exemplified by quinolone antibiotics, which bind to the DNA molecule-gyrase complex, the cleavage complex of DNA and gyrase[38], and act by stabilizing the cleavage intermediate that has a harmful effect on the bacterial DNA replication process. By inhibiting the function of the molecule-gyrase complex thereby result in bacterial cell death.[39] Alteration of the drug target by mutations, mutations that reduce drug accumulation, and plasmids that protect the cell from the effect of the antibiotic[40], are all examples of resistance to quinolone antibiotics. Gram-negative bacteria can alter their membrane permeability by changing the expression of outer membrane proteins, causing decreased accumulation of the drug[41]. The accumulation can also be decreased by the export of the drug by an increased efflux activity[42]. Both gram negative and

28 Hammond, S. M., Lambert, P. A., (1978).
29 Heikkila, A., Erkkola, R., (1994).
30 Jacobs, C., (1997).
31 Höltje, J-V., (2001).
32 Hammond, S. M., Lambert, P. A., (1978).
33 Samaha-Kfoury, J. N., Araj, G. F., (2003).
34 Dever, L. A., Dermody, T. S., (1991).
35 Jacobs, C., (1997).
36 Hawkey, P. M., (1998).
37 Hammond, S. M., Lambert, P. A., (1978), p.40.
38 United States Department of Agriculture (2006). Animal and Plant Health Inspection Service, (2006-10-12).
39 Medical Microbiology (2006). (2006-10-13).
40 Jacoby, A. J., (2005).
41 Ibid.
42 Ruiz, J., (2003).

gram-positive bacteria can protect themselves by this mechanism of mutation. Some bacteria have several efflux pumps, which effectively get rid of the antibiotic.[43] The second mechanism; the mechanism of drug target alteration, is explained by amino acid substitutions. The DNA gyrase enzyme in gram-negative bacteria and the corresponding topoisomerase IV in gram-positive bacteria are targets for this kind of mutation. The actions of these enzymes are inhibited, and the antibiotic target is changed, causing resistance to the substances.[44] Thirdly, plasmids can directly generate resistance to quinolones. The gene causing the resistance is mediated by plasmids and binds to the DNA gyrase and to the topoisomerase IV and protects the enzymes from the inhibition of the antibiotic.[45]

Protein synthesis inhibitors – antibiotic action and resistance
There are several targets, and therefore several classes of antibiotics, used to inhibit the protein synthesis in bacteria. Antibiotics bind to one subunit or in some cases both subunits on the ribosome, and the binding prevents a normal interaction between the codon on mRNA (messenger ribonucleic acid) and the anticodon on tRNA (transfer ribonucleic acid). This causes a misreading of the genetic code or results in non-functional protein complexes. Molecules of the antibiotic form complexes in the cell wall of the bacterium, which are transported to the ribosome where they bind to the 30S subunit and interfere with the binding of tRNA molecules. Other classes of antibiotics attach to the other subunit, the 50S subunit, and act by interfering with the linking of amino acids and the bonds of the polypeptide chain.[46,47,48]

Tetracycline resistant bacteria use the efflux system to pump the antibiotic out of the cell and the low amount of tetracycline enables the ribosome to proceed with the protein synthesis. Another way of bacterial protection is ribosomal alteration where a resistance gene interacts with the ribosomes protecting them against the effect of the tetracycline antibiotic. In that way, protein synthesis can continue even if a large amount of antibiotic is present in the cell. Thirdly, resistance can be expressed through modification of the antibiotic. The bacteria produce enzymes that chemically change the tetracycline and inactivate the substance.[49]

Cell metabolism inhibitors – antibiotic action and resistance
Bacteria are dependent on folic acid for cell growth. Since bacteria have to synthesize folic acid internally, the folate pathway is an appreciative target for antibiotics[50]. The combination of the synthetic antibacterial agents sulfonamides and trimethoprim[51], blocks the folic acid synthesis, and inhibits the bacterial cell metabolism from functioning properly. Sulfonamides prevent the synthesis of folic acid by inhibiting the dihydropteroate synthase enzyme[52], which reduces incorporation of para-aminobenzoic acid, *p*ABA, into folic acid. Trimethoprim antibiotic interferes with the enzyme

43 Jacoby, A. J., (2005).
44 Ruiz, J., (2003).
45 Jacoby, A. J., (2005).
46 Weisblum, B., Davies, J., (1968).
47 Hammond, S. M., Lambert, P. A., (1978), p.48-49.
48 United States Department of Agriculture (2006). Animal and Plant Health Inspection Service, (2006-10-12).
49 Weisblum, B., Davies, J., (1968).
50 Rengarajan, J. et al, (2004).
51 Houvinen, P. et al, (1995).
52 Triglia, T. et al, (1997).

dihydrofolate reductase, and interrupts its action, in that way inhibiting the folic acid synthesis.[53]

Both sulfonamides and trimethoprim have been used for many decades, but documented side effects and growing resistance to these substances have pushed back their use. One reason for the spreading resistance is plasmid-encoded resistance due to drug insensitive target enzymes dihydropteroate synthase and dihydrofolate reductase respectively. When altered, these enzymes enable the cell to continue its synthesis of folates, even in the presence of the antibiotic.[54]

2.1.3.2 Scientific research; New targets, methods and progresses

This chapter presents currently on-going research and overviews of some of the new methods that have the potential of providing us with new cures to bacterial infections or new antibiotics.

Antimicrobial peptides

Antimicrobial peptides are host defence molecules, produced mainly by multicellular plants and animals. Animals and higher plants express peptide antibiotics, defensins, which are active against bacteria, fungi and viruses. The peptides prevent infections caused by environmental microbes, on both plants and animals, and represent essential components of the immune systems in animals. The first isolated defensin is called plectasin and was isolated from a fungus. *In vitro,* the peptide is active against e.g. *Streptococcus pneumoniae*. Plectasin shows low toxicity in laboratory tests, and mice infected with *Streptococcus pneumoniae* were cured by the preparation equally successfully as by vancomycin or penicillin. Other antimicrobial peptides from multicellular organisms act by binding to cellular membranes and interrupting the membrane function, killing the targeted microbe within seconds after exposure. The killing mechanism of plectasin is slower and suggests an alternative mode of action, which is presently under investigation. However, plectasin represents a highly interesting human therapeutic candidate, and this kind of peptide also points to a possible new source for antibiotics.[55]

Bacterial interference

Colonization by some harmless bacteria, or products produced by such bacteria, can prevent colonization by harmful strains. This is called bacterial interference, and the bacterium *Lactobacillus fermentum* for instance, has shown properties that could be used to protect surgical wounds from infections. The bacterium secrets a protein, which prevents *Staphylococcus aureus* from binding to its target cells. The activity of the secreted proteins is thought to outcompete *Staphylococcus aureus* for the pathogen's binding sites in the tissue. *Staphylococcus aureus* and *Lactobacillus fermentum* both bind to the protein collagen. *Staphylococcus aureus* bind to collagen in order to stay inside the body, and the *Lactobacillus fermentum* protein prevents this action by outcompeting the pathogen for binding sites. It has not yet been established that the protective effects of the bacterial protein are due to this binding, but the method of using harmless bacteria could provide an additional feature to the search for new antibiotics.[56]

53 Smith, C. L., Powell, K. R., (2000).
54 Sköld, O., (2001).
55 Mygind, P. H. et al, (2005).
56 Strauss, E., (2000).

Genomics
New information about the molecular architecture of the bacterial cell is being obtained as a result of sequencing of bacterial genomes. Information about metabolic structures, which support the growth and viability of the cell, is revealed through this technique, increasing the number of possible new drug targets for antibiotics. Advances in the fields of functional genomics, comparative genomics and proteomics, are significant and enhance the methods for analysing genomes and therefore also for identifying possible new drug targets. The categories of targets that can be developed through combining these methods are *in vitro* targets required for viability of the cell on synthetic media, and *in vivo* targets required to establish and maintain an infection within a host organism. As the genomes of more bacterial pathogens are sequenced, it will be possible to define targets common to specific groups of pathogens, which might provide additional therapeutic techniques in the future.[57]

Natural products
Antibiotics that have been produced in the last decades mainly originate from semisynthetic preparations of natural products discovered in the 1940's and the 1950's. However, possible new natural product antibiotics from bacterial sources have lately been discovered as a result of technological advances. Efforts have particularly focused on finding new antibiotics from e.g. streptomycetes and cyanobacteria, which represent old and new sources. New antibiotics with new mechanisms of action with the potential of forming antibiotic classes, possibly targeting bacterial cells in new ways, is the result of this research. New sites for intervention in bacterial pathways are also a result of natural product research. The enzymes that catalyse the first steps in the fatty acid biosynthesis in the folate pathway may for example represent equally robust antibiotic targets as the dihydrofolate reductase or dihydropteroate synthase, which both act later in the pathway. These research results suggest that the efforts to discover natural product families may pose a way to find new antibiotics and unexploited bacterial targets.[58]

Rational drug design
Modifying existing antibiotics to make new ones is a common method for production of new preparations. A new approach, under research, aims to find the most vulnerable targets in the bacterium instead of using old targets as scaffolds. Instead of analysing bacterial genomes this method uses the structural information about the drug targets, or their natural ligands, to create new drugs, a method known as rational drug design. This method uses the pathway that coordinates cell growth and differentiation, the genetic circuitry that controls the cell cycle, to identify key points in the circuitry, which means that critical genes that control several critical functions in the cell can be found. Full understanding of the complete network of regulatory mechanisms that controls the bacterial cell is required to be able to find these key nodes. From this information and knowledge, compounds comprised of small subsets of inhibitor candidates, have been constructed that act on both gram-positive and gram-negative bacteria. The list of sensitive pathogens includes multi-drug resistant *Streptococcus*, *Staphylococcus* and *Mycobacterium tuberculosis*.[59]

57 Buysse, J. M., (2004).
58 Clardy, J., Fischbach, M. A., Walsh, C. T., (2006).
59 Powledge, T. M., (2004).

Phage therapy
Bacteriophage therapy was common in the 1930's and 1940's but became less interesting when research tools for eukaryotes were developed. However, antibiotic resistance has led to new interest in phage therapy even if there are several problems connected to this method, e.g. rapidly developing resistance. As a way to avoid these problems, a new approach to phage therapy relies on enzymes that phages produce, instead of the phages themselves. The method focuses on enzymes that phages produce to be able to break out of the host bacteria in order to infect new hosts. These enzymes can therefore be used to kill targeted organisms and *Streptococcus pneumoniae* and *Streptococcus pyogenes* are examples of such organisms. Currently, the enzymes must make contact with bacteria to be able to kill, but the next generation of engineered enzymes will hopefully be capable of killing pathogens inside cells as well. Even if phage therapy may not offer a sustainable solution, phage enzymes might constitute a temporary solution meanwhile researchers develop more durable methods.[60]

2.1.3.2.1 For the future

Statistics from PubMed show that the number of articles containing the phrase 'antibiotic resistance' increases, while the number of articles with the phrase in the title is almost constant, see Figure 4. The drop in 2006 can be explained by delayed registrations of publications in the PubMed database. Another statistic measure suggests a similar development; see Figure 5. Doubtless, antibiotic resistance is a subject of interest for many scientists[61], but the discovery and the production of new antibiotics is slow and few new drugs are expected to reach the market within the next few years. To avoid a healthcare disaster, more extensive antibacterial research is needed, as well as new perspectives on where the next generation of antibiotics will come from.

60 Powledge, T. M., (2004).
61 Levin, B. R, Rozen, D. E., (2006).

Figure 4. Publication statistics from PubMed[62]

The increasing number of articles in the database PubMed with the phrase antibiotic resistance in the article is illustrated by the blue columns. The green columns represent the number of articles with the phrase antibiotic resistance in the title.

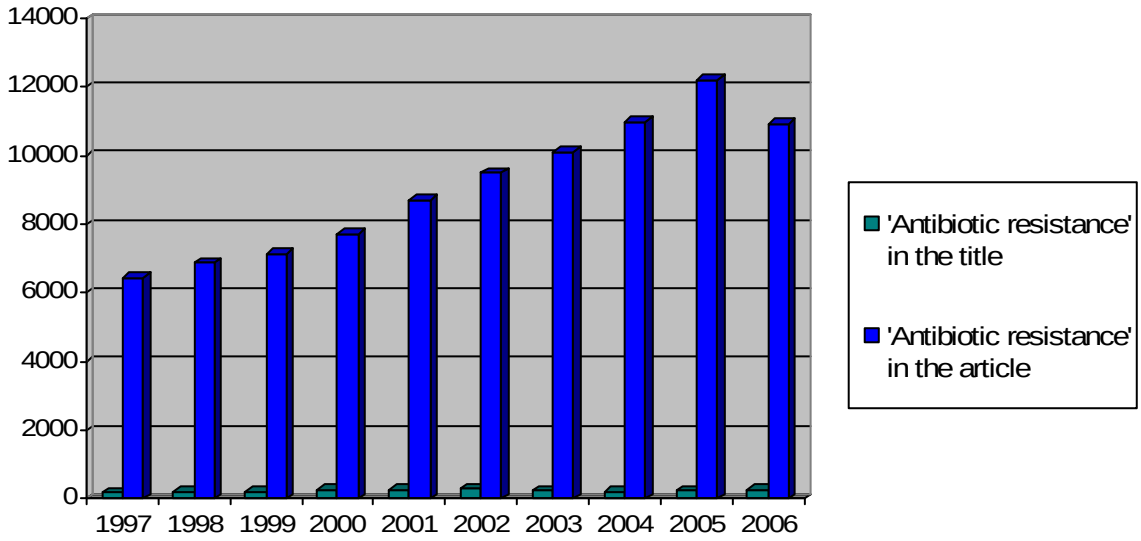
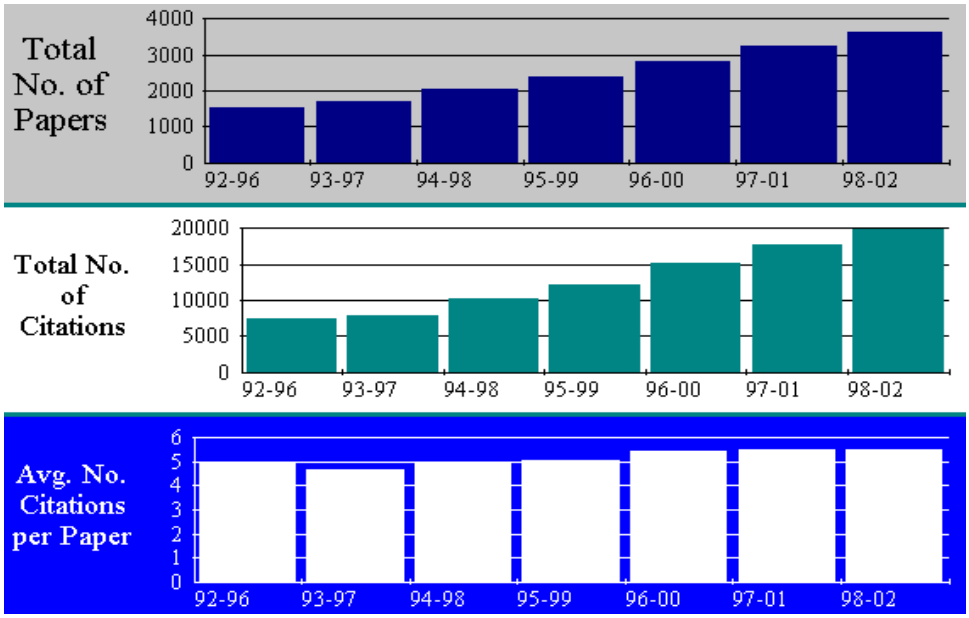


Figure 5. Publication statistics [63]

The development of papers including 'antibiotic resistance' or 'antibiotic-resistance' and the total number of citations and the average number of citations per paper.



62 PubMed (2007). (2007-04-20).
63 Essential Science Indicators (2007). (2007-01-15).

2.2 Resistance promoting factors

There are many factors that promote the emergence of antibiotic resistance, and the main aspects of this problem are connected to misuse and overuse[64]. Different kinds of misuse and overuse are fast and effective ways to increase resistant bacterial strains in the community and to endanger the opportunity for treatment of bacterial infections. It is nearly impossible to list all factors that promote resistance, since so many aspects would have to be taken into consideration to be able to fully explain the problem, e.g. economic aspects, culture, technology, history, information and education, traditions, globalization etc. Therefore a selection, of some of the main factors contributing to the growing resistance[65], is presented below and further described in the following chapters;

- Lack of diagnosis or identification of the causing agent
- Over-the-counter sales and self-medication
- Use in food and livestock production
- Hospital hygiene and administration in intensive care units
- No new antibiotics

2.2.1 Lack of diagnosis or identification of the causing agent

An issue of concern is the lack of a proper diagnosis and identification of the microbial cause of the infection. Taking an antibiotic treatment for a simple cold, a viral infection, is a waste of resources and an ineffective action since unnecessary treatments will only kill harmless bacteria and weaken the immune system against other infections. To prescribe an antibiotic in the absence of proper identification of the cause is commonly explained by time pressure or demands and expectations from the patient. Physicians that prescribes antibiotics without diagnosing the cause of the disease is a problem, often due to lack of time to discuss with the patient why the antibiotic is not needed, lack of time to wait for test results, and unrealistic expectations or direct pressure from the patient.[66] A patient demanding a cure for his or her illness is a common situation, and the high expectation of the patient getting the pills can put the doctor in a difficult position[67]. A concerned parent with a child in pain is tough to confront and in some cases a prescription is the key to comfort. Physicians prescribing antibiotics without a diagnosis is in most cases a deliberate choice, and a way to keep their relationship with the patient undamaged[68].

Colds, upper respiratory tract infections (URI) and bronchitis are conditions that typically do not benefit from antibiotic treatments[69]. Still, antibiotics are commonly prescribed for these conditions, unnecessarily. Time pressure and patient demand are two reasons why doctors prescribe antibiotics as treatments for conditions that are not normally caused by bacterial infections. Two reports that deals with the prescription of antibiotics for colds, URIs and bronchitis in the United States show that the situation is common[70,71]. Prescriptions for children and adolescence (0-18 years of age) was

64 World Health Organization (2007). (2007-02-14).
65 Ibid.
66 Schwartz, B. et al, (1997).
67 World Health Organization (2006). (2006-08-29).
68 Butler, C. C. et al, (1998).
69 Nyquist, AC. et al, (1998).
70 Ibid.
71 Gonzales, R. et al, (1997).

monitored, and out of 531 pediatric visits, patients with diagnosed colds, URIs or bronchitis, resulted in prescription for an antibiotic in 44%, 46% and 75% respectively. For adults, the results showed that out of 28,787 office visits 51%, 52% and 66% received a prescription for an antibiotic.[72,73] The numbers are presented in Figure 6. The high numbers of prescriptions illustrate the seriousness of the situation, and also the prescribing doctors' attitudes to their responsibility in the overuse of antibiotics.

Figure 6. Antibiotic prescribing for colds, URIs and bronchitis in USA

	Percentage of antibiotic prescriptions for children and adolescence:	**Percentage of antibiotic prescriptions for adults:**
Colds	44 %	51 %
URIs	46 %	52 %
Bronchitis	75 %	66 %

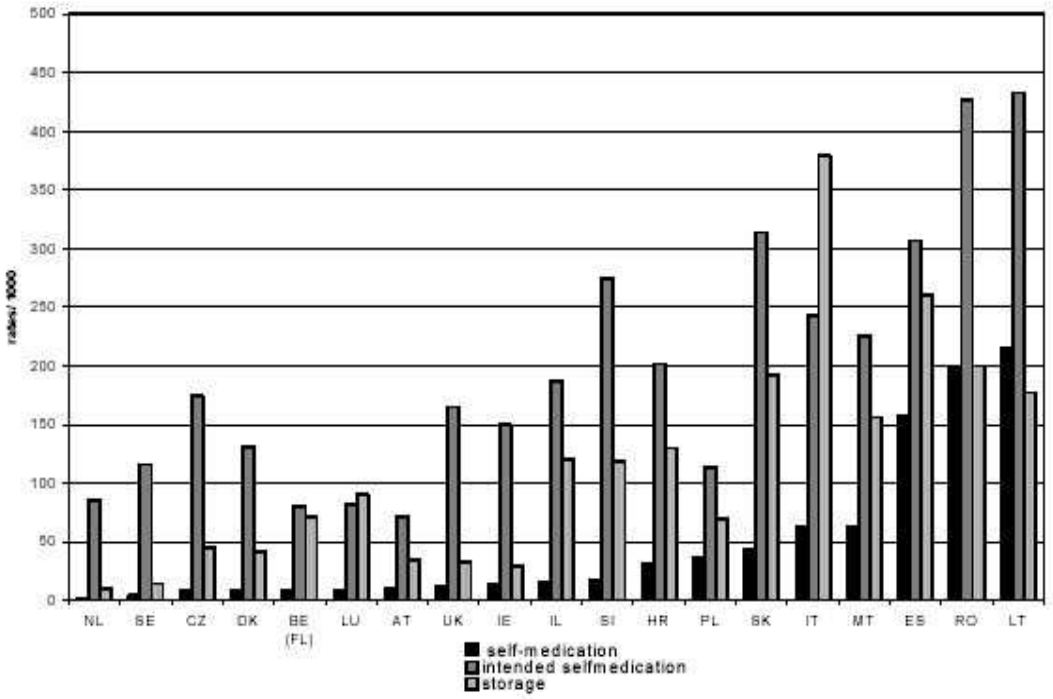
2.2.2 Over-the-counter sales and self-medication

To buy antibiotics without a prescription is a simple way to get hold of a fast treatment, but there are several risks and problems associated with this type of medical distribution. The so-called over-the-counter sales are a major problem in some countries and the number of self-medicating people is alarmingly high. A study on self-medication in Europe by Grigoryan *et al.* shows that as many as 210 per 1,000, self-medicate in eastern and southern Europe[74]. Potential self-medicating respondents in this study included those who indicated the intention to self-medicate or store drugs at home. However, the prevalence of self-medication varies extensively between countries, and the number of people self-medicating ranged from 1 to 210 of 1,000 in the study. Even if 1 out of 1,000 seems to be quite a satisfying number, the number of intended self-medications indicates a more worrying scenario. Intended self-medications ranged from 73 to 449 of 1,000, which mean that almost half of the population, in the latter case, intends to self-medicate.[75] A complete table of the use of antimicrobial drugs in the 19 countries participating in the study can be found in Appendix B. Another study conducted by the Public Health division at the European Union shows similar numbers and Figure 7 illustrates the differences between 19 European counties on self-medication, intended self-medication and storage of antibiotics[76].

72 Nyquist, AC. et al, (1998).
73 Gonzales, R. et al, (1997).
74 Grigoryan, L. et al, (2006).
75 Ibid.
76 European Commission (2006). (2006-12-12).

One contributing factor why people self-medicate is most likely the high availability of antibiotics. Over-the-counter sales without prescriptions do not only have the immediate effect of unnecessary treatment, but they also increase the risk of resistance when patients do not complete the treatment and save left-overs for future use. Inadequate dosage is a certain way to obtain bacterial resistance, as the possible harmful bacteria are not completely extinct if the user does not complete the treatment. Patients using antibiotics as precaution or using the wrong type of antibiotic also constitutes a great problem[77].

Figure 7. Actual self-medication, intended self-medication and storage in the EU.
The columns represent 19 European countries and the number of people per thousand that self- medicate, intend to self-medicate and store antibiotics.



2.2.3 Use in food and livestock production

Antibiotics can be used in livestock production therapeutically, prophylactically or as growth promoters. To use antibiotics frequently in a prophylactic purpose or as growth promoters, especially, is a risk as resistance can be obtained in certain bacteria and spread from animals, through food, and cause infections in humans.[78] The breakthrough for antibiotic use in livestock production came in the 1940's, when scientists proved that higher growth rates in animals could be achieved by adding antibiotics to the feed and water. Adding subtherapeutic doses of antibiotics to feed, became a standard, which lead to lower production costs and lower meat prices.[79] In Europe and North America, 50 % of all antimicrobial production, in tonnage, is now used for food-producing

77 Grigoryan, L. et al, (2006).
78 World Health Organization (2006). (2006-12-15).
79 Lusk, J. L. et al, (2006).

animals or poultry[80,81]. Rules concerning the use of antibiotics in food and livestock production have been issued, but still antibiotics are used for this purpose extensively worldwide[82]. The problem is that the use of antibiotics in e.g. food animals is associated with economic benefits. The risks are not as obvious but include contamination of food with drug residues, release of drug residues into the environment, the selection for antibiotic resistant bacteria, and exposure of farmers and others to antibiotics etc.[83] The primary health risk; the emergence of resistant bacterial strains, depends on that humans also commonly use some of the antibiotics used in livestock production. By routinely administering these antibiotics, the risk that bacteria will develop resistance increases. Several studies also suggest that antibiotic resistant pathogens have been transferred from animals to humans[84], for example multi-drug resistant *Salmonella*, which is thought to spread rapidly from animal to animal, creating a major health concern for humans since the bacteria causes food-borne diseases. The emerging resistance in *Salmonella* is clearly associated with the use of antibiotic agents in livestock production.[85]

2.2.4 Hospital hygiene and administration in intensive care units

Hospitals, and especially intensive care units, are breeding grounds for development and spread of antibiotic resistance by exposing a high-density patient population to heavy use of antibiotics. The risk for cross-infections is also present, due to the frequent contact between patients and the healthcare staff. Resistance increases both morbidity and mortality associated with infections and results in higher costs of care when hospital stays are prolonged, and more expensive drugs are needed.[86] A British study from 2001, illustrated that hospital-acquired infections affected 1 in 11 inpatients, carried a 13% mortality and lengthened the hospital stay two and a half times. The extra cost was concluded to be nearly £3,000 per patient.[87] Increasing numbers of hospital-acquired infections caused by antibiotic resistant pathogens depends on the selection of mutated strains from the patient's own bacterial flora during an antibiotic treatment, or on the transfer between bacterial plasmids or transposons, which results in that resistant strains subsequently spread among patients in the unit or in the hospital, with the potential of causing epidemics. The increasing numbers of hospital-acquired infections also depend on medical management. By using monotherapy instead of combination therapy, selection for resistance in certain infections might be favored. Transmission of resistant strains also occurs when patients get in contact with contaminated hands of the healthcare staff. [88] Basic infection control, such as hand washing, is known to be poor in many hospitals, and lack of time, poor availability of sinks and soaps and skin sensitivity are frequent healthcare staff explanations for this behavior[89]. To reduce hospital-acquired infections and antibiotic resistance in the hospital setting, improved surveillance, optimal prescribing and increase of basic infection control, is needed.[90,91]

80 World Health Organization (2006). (2006-12-15).
81 European Commission (2007). (2007-02-13).
82 Ibid.
83 Rajic, A. et al, (2006).
84 Lusk, J. L. et al, (2006).
85 Bauer-Garland, J. et al, (2006).
86 Struelens, M. J., (1998).
87 Stone, S., (2001).
88 Struelens, M. J., (1998).
89 Stone, S., (2001).
90 Ibid.
91 Norrby, R. S., (1996).

2.2.5 No new production

Twenty tears ago, the pharmaceutical industry brought approximately five new antibiotics to the market every year. Now, the number of commercialized new antibiotics is one or two a year. A study from 2004 reported only six antibacterial drugs out of more than five hundred drugs, in late-stage clinical testings in large pharmaceutical firms. The reason for the lack of new compounds in development is mainly economical. Antibiotics cure patients, rather than treat, and the short period of use makes antibiotic preparations less attractive than drugs for chronic diseases. Also, patent lifetimes and drug resistance restrict the commercial life of an antibiotic to 8-10 years.[92] Researchers have concluded that the bottleneck, in the process of developing and introducing new antibiotics to the market, is the drop-out by the big pharmaceutical firms. The big companies have the finance to develop these kinds of preparations, but instead they leave the development to small biotech firms, which slow down the process.[93] Several solutions have been proposed as attempts to keep up the rate of development and the interest from drug companies, e.g. new standards for approval of antibiotics or tax breaks for work on antibiotic drugs[94].

2.3 Network initiatives and engagements

Several strategies have been proposed to influence the situation with misuse and overuse. Vaccines, strict application of therapeutic guidelines, and prevention or restrictive use, have been suggested as ways to slow down the emergence of antibiotic resistance, but actual results from activities and actions are not showing a satisfactory result. Surveillance programs and education of clinicians, pharmacists, veterinarians, drug company representatives and consumers, are methods aiming to impact the misuse of antibiotics.[95]

There are several large networks and organizations already working with these questions and many projects are on-going today, where surveillance projects are among the most common. For example the World Health Organization and the European Union are both engaged in the matter and several projects are now in progress[96,97]. These projects are covering many areas of the problem but the consumer questions do not get as much attention as others. There are many other networks and organizations that are working with antibiotic resistance e.g. STRAMA (The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents), APUA (Alliance for the Prudent Use of Antibiotics) and FDA (U. S. Food and Drug Administration), which all are dealing with different kinds of education and information.

92 Editorial, (2006).
93 Powledge, T. M, (2004).
94 Pearson, H., (2006).
95 Bergeron, M. G., Ouellette, M., (1998).
96 World Health Organization (2007). (2007-03-06).
97 European Commission (2007). (2007-03-06).

3 Materials and method

3.1 Project initiative

In order to define this project, discussions with representatives from Swedish consumer organizations, international health activists and supervisors were carried out to gain insight into various aspects of the problem with antibiotic resistance. By compiling information from discussions, articles and other literature, and Internet searches on e.g. PubMed, ISI Web of Knowledge, Blackwell Synergy and Ingenta Connect (using key words like *antibiotic resistance, antimicrobial resistance, rational drug use, bacterial infections, misuse of medicine* etc.), the basis and starting point of the project was specified. The articles, web pages and other written material referred to in this report are used after my personal judgment to obtain convincing and reliable information. References, quotation index, University status, status of the publication, were, among others, factors I considered in order to establish credibility of the report.

3.2 Design

In order to reach international organizations as easy and fast as possible, it was decided that a questionnaire should be distributed by e-mail. What kind of information needed to complete the survey was discussed as formulation and reformulations of the informational letter of the questionnaire and possible questions, were conferred with supervisors and contact persons at two Swedish consumer organizations; Consumer Institute for Medicine and Health (KILEN) and Konsumentföreningen Stockholm, and with the People's Health Movement (PHM). A combination of multiple choice questions and open questions concerning the situation and the awareness was the final result. The purpose of asking questions concerning the previous, current and future interest in antibiotic resistance and awareness, was to be able to present a qualitative overview of the global situation seen from the grassroots organizations' point of view. For the questionnaire in full, see Appendix C.

Another indirect function with distributing the questionnaire was to raise a thought and possibly even an interest in the subject, even if the organization receiving the questionnaire, chose not to reply.

3.3 Participants

To select organizations to include in the study, a large international network of organizations of different kinds and nationalities was searched for, to constitute the centre of the contact net. One of the largest umbrella organizations for consumers in Europe, Consumers International[*], led me to the People's Health Movement (PHM)[**].

PHM was formed after the People's Health Assembly in year 2000 when people's organizations, civil society organizations, NGOs, social activists, health professionals, academics and researchers came together from 75 countries to make a statement against the continuing and growing inequities in health, despite the promises of the Alma Ata declaration in 1978[***],[98] and to discuss how to obtain health for all. The People's

* www.consumersinternational.org
** http://phmovement.org
*** The Alma Ata declaration in 1978 proclaimed that an acceptable level of health for all people should be obtained by year 2000.

Charter for Health was created, and is the most widely endorsed consensus document on health since the Alma Ata declaration.[99]

Since PHM was built on international grassroots organizations, and comprise local, national and international organizations[100], I decided to let PHM represent the central node of the contact net and the starting point of the survey. To map organizations and networks worldwide, the eight international umbrella organizations, constituting the eight sections of PHM were used[101]:

- *Asian Community Health Action Network*
- *Consumers International*
- *Dag Hammarskjöld Foundation*
- *Gonoshastaya Kendra*
- *Health Action International*
- *International People's Health Council*
- *Third World Network*
- *Women's Global Network for Reproductive Rights*

Members, member organizations and affiliates of these organizations were also contacted, either directly or through a representative of the umbrella organization, and included in the study. The contact net is illustrated in Figure 8. An infinite quantity of organizations was the reason for limiting the mapping to these organizations. The organizations' websites, and Internet searches, were mainly used to find contact details to member organizations and networks. A few contacts were received through supervisors, Ravi Narayan (PHM)[*], Mary Murray (ReAct), Lena Westin (Consumer Institute for Medicine and Health - KILEN), Louise Ungerth (Konsumentföreningen Stockholm), and from the participant list of the What Next Forum[**].

Focusing solely on organizations at the grass root level was a way of attempting to obtain a result illustrating the interest of the actual users – the public. These kinds of organizations may also be possible means to constitute the foundation for a global action of awareness since they are powerful in both quantity and engagement, which further motivates the focus.

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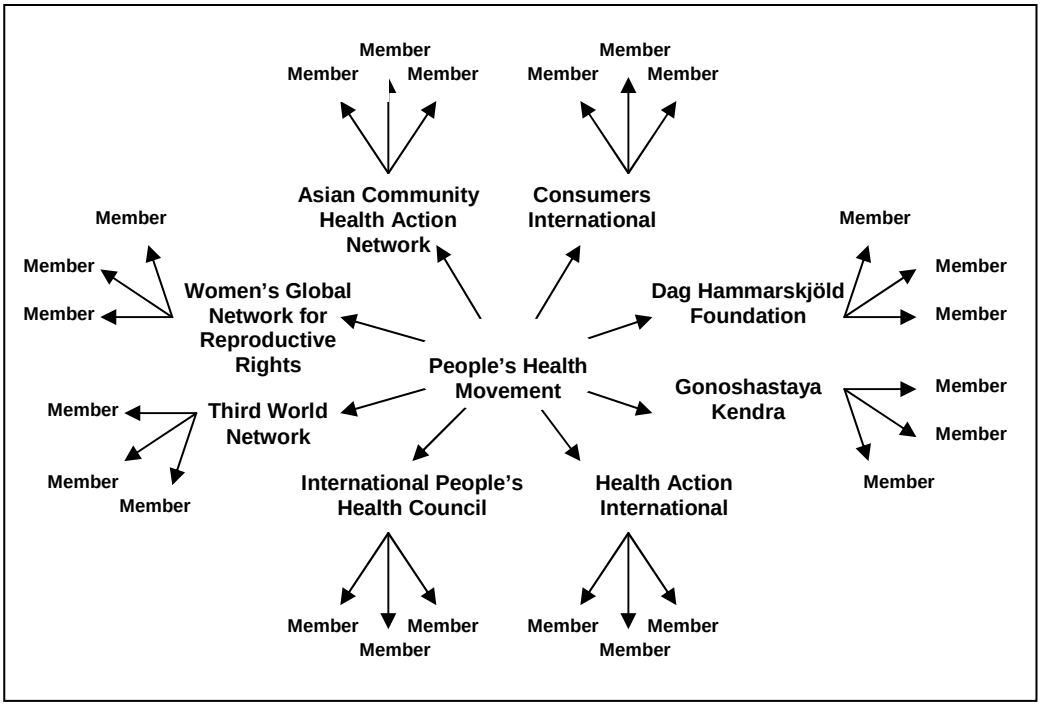
98 World Health Organization (2006). (2006-12-10).
99 People's Health Movement (2006). (2006-12-14).
100 Ibid.
101 People's Health Movement (2006). (2006-12-16).
* One of India's leading public health activist, who also has been coordinator of the People's Health Movement.
** What Next Forum, arranged by the Dag Hammarskjöld Foundation, took place at Uppsala Castle 19-21 September 2006 when global changes in health, science, technology, economy, politics etc. were presented and discussed. More info at www.dhf.uu.se/whatnext/forum/

Figure 8. The contact net; People's Health Movement with affiliates and members



3.4 Data collection and analysis

The first dispatch of the questionnaire was sent out on October 30 and October 31, to 250 international organizations and networks. The mail included an information letter describing the survey and giving a brief background to the subject, the 6 questions (of which some included attendant questions) and an attached document explaining the mission and vision of ReAct, see Appendix D.

The latest preferred answering date was set to November 8, and November 9 respectively, giving the organizations ten days to answer. The first reminder was sent out by November 15, the second on December 6, the third on January 20, and the survey was closed and decided to be finished on January 31.

The e-mail responses were compiled and the answers to the multiple-choice questions, 4a-4c, were counted and are reported in chapter 4.1. The responses to question 5, were compiled and are presented in chapter 4.2. When compiling the answers to question 6a and 6b, several categories were used to define different areas of similar character. Further analysis of the answers resulted in more specific divisions according to my personal opinions and the final result is presented in chapter 4.2.1 and 4.2.2.

4 Results

After the first dispatch of the questionnaire, by November 15, thirty-five answers had been received. A total of 54 responses had been received after the total of three reminders, constituting 22% of the 250 contacted organizations and networks. Twenty-five organizations responded to the e-mail but did not answer the questions due to primarily lack of time or knowledge. Two organizations replied without having filled in the questionnaire, but still wanted to be informed about the survey and possibly participating in future actions and collaborations. These organizations are not included in the statistics. Two organizations, out of the 54 responding organizations, had not heard about antibiotic resistance before, which means that 96% had heard of it before. Appendix E contains tables of the results, in numbers and in percentages, from questions 4a-4c. The responding organizations and networks are listed in Appendix F and are divided according to continent and thereafter in alphabetical order.

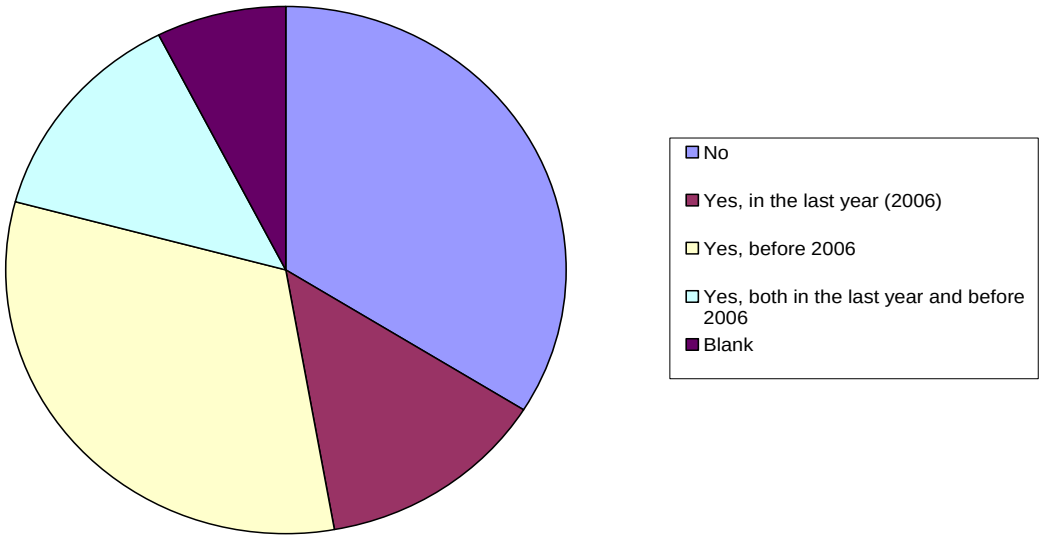
To monitor the organizations' opinions on the problem of antibiotic resistance, questions about the use, access and side effects were included in the questionnaire. The organizations were also given the opportunity to add other opinions on the matter that did not fall under any of these categories. However, the majority of the respondents chose not to add new categories, which resulted in responses connected only to the given aspects. The main issues concerning antibiotic resistance described by the organizations and networks are presented below and further discussed in chapter 5.1;

- The bad use of antibiotics
- The easy access
- The overlooked side effects

4.1 Previous, current and future engagements

Previous studies monitoring the opinions of consumer organizations, and networks, have not been found and indicate that these are unexplored groups. This survey shows that these kinds of organizations are engaged in questions related to antibiotics and in many cases work with direct advocacy. However, responses to the question "Have you previously worked with questions related to antibiotics?" indicate that there has previously been a greater engagement from the organizations in antibiotic resistance related questions than there is today, see Figure 9.

Figure 9. Questionnaire result - Previous engagement

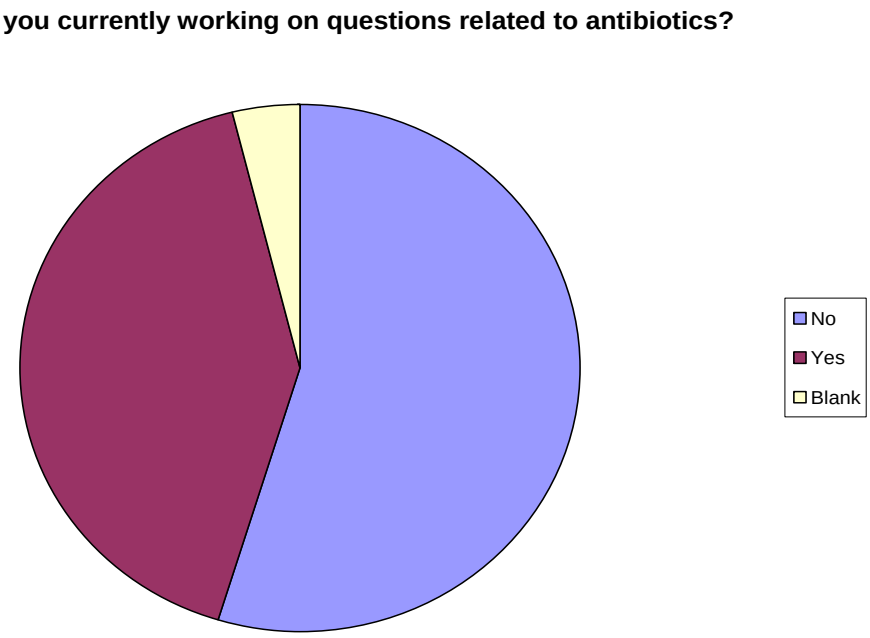


The work that the organizations previously had been involved in concerned:

- Studies of antibiotic use
- Publication of information to members
- Production of fact-sheets
- Organizing meetings concerning antibiotic resistance
- Food controls
- Research projects on medical use and publication of the results
- Studies on alternative treatments
- Support of other organizations working with antibiotic resistance
- Promoting legislation to ban use in livestock
- Work with related questions e.g. AIDS
- Work concerning the public health in developing countries
- Drug pricing
- Work trying to decrease the irrational use of drugs by general practitioners
- Studies on side-effects of antibiotics
- Publication of books
- Press-releases

The result illustrated in Figure 9, is underlined by the responses to the next question of the survey “Are you currently working with questions related to antibiotics?” where the majority of the respondents answered “No”, see Figure 10.

Figure 10. Questionnaire result - Current engagement

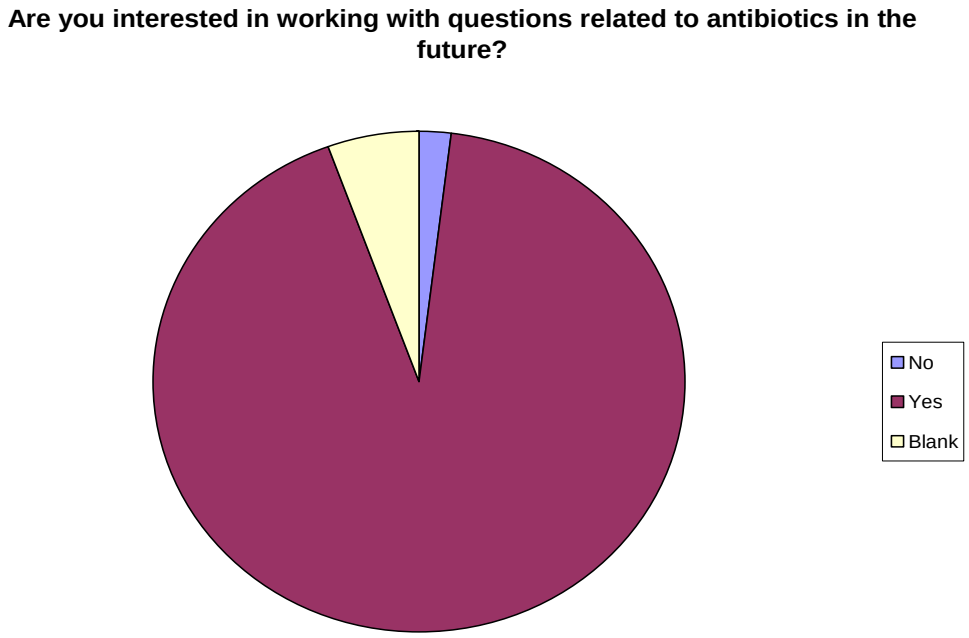


The engagements that the organizations currently are involved in concerns:

- Promotion of prudent use
- Arranging and attending workshops
- Promotion of legislation concerning veterinarian and livestock drug use
- Education of consumers
- Publish articles
- Research
- Development of new antibiotics for tuberculosis
- Overall rational drug use work
- Participation in EU dialogues
- Working with the problem with over-the-counter sales and irrational prescribing
- Increasing the availability and access at public health sector facilities
- Prevention of hospital-acquired infections
- Education of consumers on proper use

When asking the organizations about their interest in working with antibiotic related questions in the future, Figure 11, the majority answered “Yes”.

Figure 11. Questionnaire result - Future engagement



The interest in working with these kinds of questions in the future concerns:

- Adaptation to WHO modules
- Target work on the prescribers and the dispensers
- Bring out publications for laypersons and medical professionals
- Produce consumer related information
- Intervention of government regulatory
- Increase the consumer awareness by increased information distribution
- Improving communication with patients
- Closer collaboration with other organizations
- Legislation advocacy concerning e.g. over-the-counter sales
- Develop new antibiotics
- Campaigning to introduce the same standard across the whole European Union concerning the use of antibiotics in animals and food
- Arranging workshops
- Education of consumers and health professionals
- Promoting work on food safety
- Banning the use in agriculture
- Sample products on the market to reassure a good quality

4.2 The importance of raising awareness

When the questionnaire answers had been compiled, it was evident that raising the awareness with different groups in society is an important issue to the respondents. Alternatives were given to monitor the opinions of some of the main groups in society concerned in antibiotic related questions. The alternatives were also given to prepare the respondents for the following question concerning ways to raise this kind of awareness. The alternatives presented in the questionnaire of different groups possibly important to raise awareness with, were doctors, health professionals and consumers. The answers show that 94% of the organizations think that it is important to raise the awareness of

antibiotic resistance with doctors, 94% with health professionals while the percentage of the importance of raising awareness with consumers is 100%.

4.2.1 How can awareness be raised?

The suggestions on how awareness of antibiotic resistance can be raised with the groups presented in the previous chapter are numerous, and they are divided into categories below. Common answers include education of different groups of people, advocacy through media, monitoring and legislative suggestions, but the most common answer concerns the importance of providing information, particularly to the consumers.

Education and information

- Educate pharmacy students and other medical students during their education
- Conducting seminars
- Provide doctors and consumers with appropriate information
- Conduct awareness workshops
- Educate the public through campaigns
- Provide consumers with proper information when antibiotics are prescribed
- Let consumers inform other consumers
- Educate children in schools
- Information through manuals, leaflets, posters, books
- Publications in regional languages
- Articles in newspapers
- Information through television and webpages
- Factsheets online for consumers
- Press releases
- Newsletters

Surveillance and promotion of legislations

- Study the factors promoting resistance
- Increase food controls
- Monitor the spread of self-medication and unnecessary prescriptions
- Survey patient knowledge
- Laws on prescriptions
- Policy dialogue with decision makers
- Prevent self-medication
- Laws on use in livestock production and in veterinarian use

Other suggestions included getting professionals to lead information campaigns, provide patients with medical alternatives, use cultural settings to increase awareness, and collaborations between NGOs.

4.2.2 Suggestions and ideas for organizational engagements

There is a big interest and willingness in participating to raise awareness. Most part of the organizations want to participate in such engagements, see Figure 12, and the ideas on how to do this are presented below and represent the suggestions that the organizations think can contribute to the process of increasing the awareness.

Figure 12. Participation interest

Would your organization be willing to participate in such awareness raising?		
Yes	45	83%
No	1	2%
Blank	8	15%
	= 54 organizations	*= 100%*

Education and information

- Initiate and lead campaigns
- Make guidelines to patients
- Publish leaflets and books in several languages
- Inform about alternatives to antibiotic use
- Train health professionals
- Inform consumers through articles, Internet, books
- Conduct seminars, workshops and awareness programs
- Educate doctors and medical students
- Make programs on medication use
- Present case studies on the web
- Provide media contact

Surveillance and promotion of legislations

- Study the factors influencing bad use
- Make risk assessments of misuse
- Campaign to ban use in livestock production and agriculture
- Promote regulatory improvements

Networking

- Joint declarations
- Work together with health networks, consumer organizations, NGOs and authorities
- Engage in international actions

5 Discussion

5.1 Result discussion

5.1.1 The factors

The use of antibiotics
When asking the organizations and networks what they believe to be the main issues concerning the use that are promoting resistance, the factors that were most frequently described by the organizations were; over-prescribing and dispensing, over-the-counter sales, overuse in livestock and food production, lack of knowledge and information to different groups in society. When describing the problem of unnecessary prescriptions, the responsibility of the doctor or pharmacist was commonly questioned. The problem of antibiotics that are prescribed without identification of the infecting organism is a frequently recurrent situation. Therefore, antibiotics are often prescribed to treat viral infections, like common colds, which is unnecessary and ineffective. It was also mentioned that doctors are prescribing the wrong antibiotic to patients, some of which are reserved for certain infections, as newer ones are more expensive to buy, resulting in a bigger profit to the clinic, and that patients often regard the newer antibiotics to be better. Prescription can thereby become a matter of profitability. Co-operations between pharmaceutical companies and hospitals or clinics, can provide doctors with payments in exchange for using their antibiotic preparations, which adds to the normal salary. This leads to not only prescription without diagnosis, but to an extensive over-prescribing situation. Over-prescribing antibiotics can in these cases become a matter of private profitability putting the apprehension of resistance at second place. In pharmacies where antibiotics can be bought without prescriptions, the principle of good business rules: the more sales the better business. Knowledge of antibiotic resistance is therefore not a guarantee for increased caution of using antibiotics neither for doctors prescribing medications or sales people in pharmacies.

The situation described above is also a matter of consumer awareness, or to be more exact; the lack of it. Many of the respondents describe the lack of knowledge of the consumers, and the lack of information directed to the consumers, as one of the main problems. Because of the lack of information and knowledge, many patients also self-medicate, which often results in inappropriate use such as interrupting a course of treatment too early. It can also result in the perception that antibiotics can be used as a precaution, which is further used by economically driven sales persons and pharmacists as a way to sell more antibiotics as dispensing regulations are missing in many countries. The opportunity to self-medicate is golden as patients easily can buy their own prescription-free antibiotic over-the-counter. This is a common situation that is exploiting the lack of awareness of the consumers and endangers the effect of antibiotics, in order for the pharmacist or sales person to complete another purchase. Another major problem described by the organizations is the use of antibiotics in livestock and animal production. The use of antibiotics in animal feed is often unnecessary and the risk of spreading resistance to humans through food products is a great concern. Antibiotics are commonly used as growth promoters and excreted into the environment, which increases the risk of spreading resistant strains to humans. There is also a problem with over use in veterinarian use. Same as for humans, the lack of identification and cause of the infection, is a big problem and a great promoter for

resistance. Lack of knowledge and information is letting this kind of use continue. These examples of irrational use are factors that are promoting resistance to grow today.

Other factors described by the organizations were; the slow production of new antibiotics, the problem with counterfeit antibiotics with poor quality, overall legislation problems, and the rising costs of antibiotics in some countries.

The access to antibiotics
The access to antibiotics is in the majority of the described cases good, in fact too good. A common response to this question deals with the easy access to antibiotics through unnecessary prescribing of antibiotics or over-the-counter sales of the preparations, responses also frequently occurring to the last question concerning the use. A few organizations also mentioned that the over prescribing situation in some cases are due to pressure on the prescribing doctor or pharmacist from pharmaceutical sales representatives and not only because of their private profit making. Even if the problem of growing resistance is largely due to the easy access to antibiotics some organizations described that the access sometimes is limited and poses a problem in that way. This problem does not promote resistance directly, but patients in need of antibiotics in e.g. rural areas where proper antibiotics are not available, might end up using counterfeit antibiotics or expired preparations, which in that way indirectly promotes resistance. Another problem with unavailability is the high costs. In some areas newer antibiotics are mainly sold and large groups of the population does not afford these drugs, leaving the above mentioned alternatives, like counterfeit or expired antibiotics, to these groups of people.

Other factors that the organizations recognized as problems concerning the access to antibiotics were e.g. the lack of legislations when dealing with antibiotics and the easy access of antibiotics as growth promoters in livestock production.

The side effects
The result of the survey shows that many organizations consider the lack of surveillance programs for side effects of antibiotics to be a problem. The respondents know that side effects occur but in many places the knowledge about the exact effects and the extent of the side effects is not sufficient. Possible reasons for this are the lack of surveillance programs as mentioned earlier but the ignorance of side effects are also of great concern. Both consumers and prescribing doctors are often not enough aware or concerned about this issue and by prescribing an antibiotic unnecessarily the patient will only experience the side effects without any health benefits. Examples of side effects described by the respondents are; allergic reactions, diarrhoea, skin itches, nausea, vomiting, anaemia, organ failure etc., and more consumer information about these effects are needed since the effects are relatively unknown to the users.

Other issues described by the organizations concerning side effects are the problem with residues of antibiotics in foods, the unawareness of side effects when interacting antibiotics with other drugs, the overuse in young patients, the economic effect on the healthcare, and the impact on the environment.

Other aspects related to antibiotics
To give the organizations space to bring out aspects related to antibiotics that does not fall under the previous categories, an open question was added to the questionnaire. The

majority of the respondents did not respond to this question, but a few organizations added issues that are related to antibiotics, for example the need for a global response, alternative medications e.g. by homeopathy, strict control when introducing new antibiotics and the unnecessary increase of public spending on healthcare.

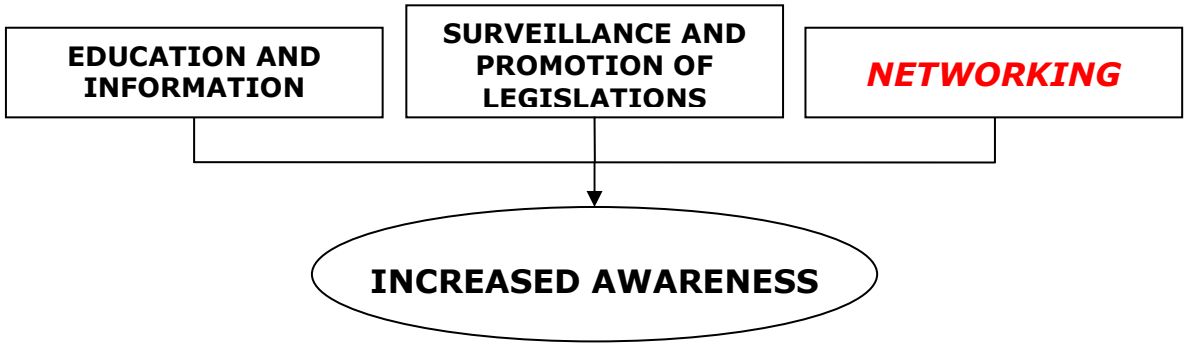
5.1.2 The interest, the engagements, and the future

A larger proportion of the organizations had worked with antibiotic resistance related questions previously, than the proportion that is currently working with these issues. A tendency to more surveillance related engagements can be seen in the previous work as current engagements tend to focus more on the education and information, but in general, consumer oriented information constitutes the core of the work in both cases.

The answers to the question concerning the interest are unanimous, and the absolute most part of the organizations participating agrees on this matter. The responses concerning the interest tend to focus on consumer information and introduction of regulatory standards, among other suggestions and ideas. A percentage of 92% showing interest in working with antibiotic related issues in the future, and 83% wanting to participate in awareness raising, are high numbers, but the number of organizations actually working with these questions have decreased in the last year (2006), which might seem somewhat contradictory. To investigate what this depends on is therefore important as the number of engaged organizations need to increase instead of the opposite.

The suggestions on how awareness can be raised and ideas on how the organizations want to participate to change the situation were similar, and concern distribution of information, education of different groups of professionals and laypersons and legislation related issues. A difference between the suggestions and the actual ideas on how to participate in the awareness raising is that more responses, in the latter case, concern the willingness of collaborating with other organizations and work together to make a change. As a conclusion, three main factors, or groups of ideas, may constitute a way to increase the awareness of antibiotic resistance, see Figure 13.

Figure 12. Three possible main factors increasing the awareness



There is however no doubt that there is a great interest in the subject and a willingness of changing the situation. The interest is however strongly connected to the consumer

organizations' and networks' point of views, and a survey including other kinds of organizations would represent a more complete picture of the global interest in questions of this kind. Joint declarations could be a possible way to use the quantity of the consumer organizations to possibly influence and persuade authorities to introduce more strict regulations and better processes of prescribing and selling antibiotics. It is unknown how large difference this kind of collaboration between different areas of the world would amount to, but if the organizations would commit to the ideas they have stated, they can hopefully contribute to a positive change in the understanding of the problem and to change attitudes, which are promoting resistance today.

5.2 Methodological discussion

The selection of organizations and networks
According to several studies on response rate of mail surveys, the estimated response percentage of an Internet survey of this kind is about 20-30 %[102,103]. The response rate in this survey was 22%. A higher response rate could have been achieved but a limiting factor is time as additional reminders and reminder phone calls surely could have increased the participation number. Also, several of the umbrella organizations, see Figure 8 in chapter 3.3, did not participate in the survey, which decreased the participation immediately because of the broken link between them and their members. Their members were however contacted directly and invited to take part in the survey. In some cases the participating umbrella organizations encouraged their members to answer the questionnaire, which increased the response rate.

The choice of letting PHM act as the central node, motivation in chapter 3.3, did not result in a statistically representative outcome. The influence of PHM differs between continents and countries and therefore the result is not to be generalized. Also, the organizations working with PHM may not be representative for the general consumer organization as interests and values might have been adjusted to suit each others' agendas.

The result of the questionnaire
As mentioned above, the selection of participating organizations is biased, and the same is therefore applicable to the results from the questionnaire. The answers naturally depend on the type of organization. Other engagements, resistance promoting factors, suggestions and interests, might have been received with a different selection of consumer organizations. As for the questionnaire, the majority of the organizations responding were already involved in the subject of antibiotic resistance. Perhaps a large group of organizations, not involved in these questions, decided not to respond despite the invitation directed especially to organizations not already committed to this kind of work. To better get in contact with these organizations, the questions could have been distributed in two rounds with the first intended to establish the degree of involvement. The possible falling-off would mean a big loss of potential as these organizations would have the possibility of introducing antibiotic resistance as a new issue on their agenda.

The actual answers to the questionnaire must also be interpreted with caution. For example, the main factors promoting resistance described by the respondents are

102 Kaplowitz, M. D., et al, (2004).
103 Cole, S. T., (2005).

strongly dependent on the given categories. Other groups of factors might have been described if a completely open question had been used to examine this issue. The reason for presenting the organizations with categories was to increase the answer frequency, as open questions are easier to leave unanswered and to receive data possible to summarize.

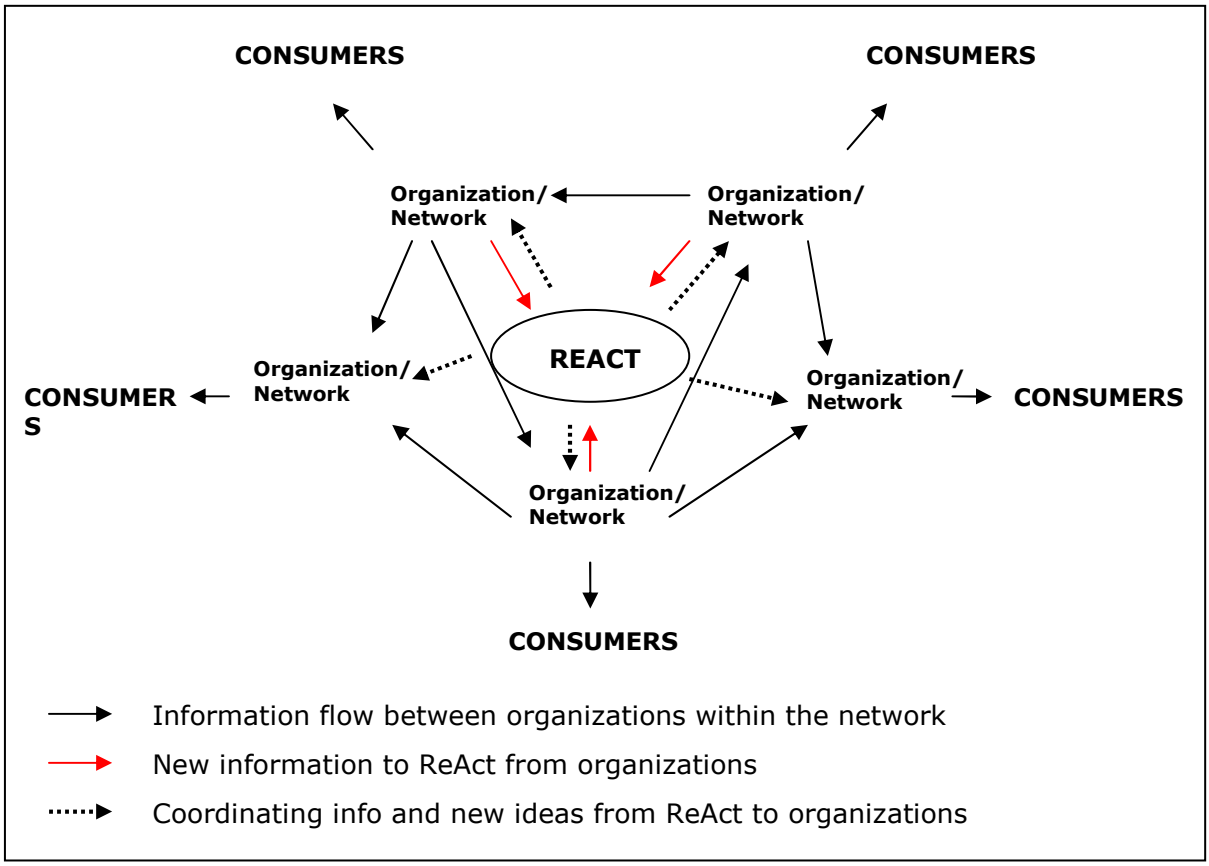
5.3 Implications and conclusions

The factors that the organizations and networks recognize as the main issues promoting resistance are described from the consumer's point of view in this report and the result will surely differ if asking other kinds of organizations similar questions. There are unlimited numbers of factors affecting the situation and the answers received from this questionnaire are only grasping the problematic constellation of correlated causes. However, the factors concluded from the answers agree with resistance promoting factors described in literature, and they appear to be general issues when explaining the problem of the growing resistance. The result does not qualify as a quantitative statistical survey due to the biased selection of participating organizations and networks, but the result can be seen as a qualitative description of international views and opinions on the matter. The bad use, the easy access, and the lack of laws and regulations are the main factors, which the organizations generally believed to be the most important aspects to consider. Many variations of these aspects were described by the organizations, but in summary, they represent the primary causes to the increasing antibiotic resistance.

To be able to reach out with information concerning the causes and with consumer recommendations, the organization or network requires a great understanding and knowledge of what kind of information the consumers need. Ideas on how to spread the information and ways to communicate with the consumers could possibly be distributed with the help of a network. The network also constitutes a means for professionals and activists to meet and to share thoughts on possible solutions with peers. To reach out further than the local setting, a network might represent a link between distant areas, providing a larger group of people with information and support.

A difficulty, when forming a network aiming to join other networks and organizations, is to realize what missing part to play. What does other networks and organizations need in their effort and how can this be provided? A network like ReAct needs to find a role in the work towards decreasing the resistance that will engage other networks and organizations to join. To accomplish this, the network must be sure of what function they want to have and what they want to achieve with their work. Internal uncertainty within the network will impede the message from reaching out, and other organizations and networks may become unsure of the credibility of the network. This study has shown that there is a great interest and that something, or someone, has to catalyze the process of educating the consumers on a global level. To take advantage of this interest, an analysis of what kind of support and help the organizations need, should be made to get to the bottom of how much potential they possess. When clarified what they need, a coordinating network might possibly constitute a source of support and ideas, which would help the organizations to proceed with their work informing consumers and find new ways and solutions. A model of information distribution and possible flows of ideas between ReAct and consumer organizations and networks is illustrated in Figure 15.

Figure 15. Information distribution between consumer organizations/ networks and ReAct



When drafting new members and growing in size, it is crucial to consider all parts of the network during the process. Growing too fast without a solid base might result in an organization without the ability of maintaining the focus on the purpose and without the sincerity set out from the beginning. Another aspect of great importance is to keep focus on the target group. Diverging from this focus may appear confusing as the information to different groups might need to be presented in different ways. With a clear focus, an attainable goal and a solid organization, the possibilities of finding a way to influence the situation and of succeeding as a network, may increase.

The interest in raising awareness is, without a doubt, high, and the consumer organizations may possess a great power to affect the situation, but an international collaboration between the organizations concerned, is necessary to be able to utilise their full capacity when distributing information and convincing policy makers and consumers to change their behaviour and attitudes. The result from the questionnaire implicate that collaboration between organizations is necessary, and several organizations listed ideas on cooperation as actual ways of participating in a global campaign. Interestingly, few organizations listed collaboration as a possible way to raise awareness, but when asked about actual ways to participate in awareness raising, several organizations mentioned international cooperation as an alternative. Without organization and concurring goals, valuable time will pass before results will be

achieved, but assuming and hoping that the interest can be transferred into action, there are great possibilities for organizations and networks of this kind, to influence the situation.

5.4 Future research

- To be able to fully generalize the global interest and what is being done about the problem, a survey of other proportions would be required. A more correctly performed statistical analysis and a survey selection representing the continents and nations fairly, would yield a result possible to generalize and interpret more exactly.

- As for the interest, a more thorough survey of the factors promoting resistance could increase the understanding of the problem. The differences between areas could be studied as a way to map the dispersion of the different factors connected to local traditions and customary behaviours.

- By analysing the organisational structure and internal activities of a network, an organization, like ReAct, could discover ways to raise awareness and to distribute information efficiently.

- If the result from the questionnaire agrees with reality, the consumer organizations' engagements in questions related to antibiotics have decreased in the last year, and an investigation should, in that case, be made to understand why this is.

- Consumer organizations and networks differ in size, goals, work methods, engagement etc., and a more complete analysis of these differences could disclose the potentials and possibilities of the different kinds of organizations in order for them to attack the problem effectively considering their position, and to be able to cooperate with other organizations successfully.

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Appendices

A. Overview of the bacterial cell

Bacterial cell wall synthesis

The cell wall maintains the shape of the cell and prevents the cell from bursting of osmotic pressure. The pressure is due to the high concentration of ions and metabolites inside the cell compared to the surrounding medium, and in order for the bacterial cell to function normally in terms of growth, division etc., the high concentrations are required.[104,105] The major constituent of the bacterial cell wall, and one of the most important constituents, is peptidoglycan. This material consists of alternating N-acetylglucosamine (NAG) and N-acetylmuramic disaccharide (NAM), cross-linked by transpeptidase enzymes, creating a rigid cell wall. Put together, the sugar polymers form a molecular network which protects the cell.[106] The amount of peptidoglycan in bacterial cell walls can function as a way to identify different bacteria. Gram staining technique is used to separate bacterial species into two groups, gram-positive and gram-negative, by observing differences in the cell walls. Cell walls of gram-negative bacteria* are structurally more complex than gram-positive**. The outer membrane contains lipopolysaccharides, often toxic, which makes the gram-negative bacteria generally more pathogenic than the gram-positive bacteria.[107]

Bacterial nucleic acids

Chromosomes carry the genetic information in all living cells, and the specific regions containing the information, the genes, are composed of deoxyribonucleic acid (DNA). The other type of nucleic acid, the ribonucleic acid (RNA) occurs in three forms; messenger RNA, ribosomal RNA and transfer RNA, and they are involved in the expression of the gene. DNA and RNA are polymers of nucleotides which consist of a nitrogenous base (pyrimidines or purins), a five-carbon sugar and a phosphate group. DNA consists of two polynucleotide chains formed as a helix, held together by highly specific hydrogen bonds. DNA gyrase is an enzyme that controls the folding or supercoiling of the DNA during DNA replication.[108,109] It is essential for preventing the DNA molecule from becoming entangled during replication of circular chromosomes in bacteria. RNA is a single polynucleotide chain which is folded several times, in a less specific way than DNA, forming loops.[110,111]

Providing directions for self-duplication during cell division and information transmitting, and mediate controlling the metabolic activity of the cell are the main functions of DNA. Replication, DNA biosynthesis, transcription and mRNA biosynthesis, mediate these functions. During DNA replication the two strands of the

104 Hammond, S. M., Lambert, P. A., (1978), p.20.
105 Campbell, N., Reece, J.,(2002), p.528.
106 Meroueh, S. O., et al, (2006).
* After treatment of crystal violet dye, iodine solution and organic dissolvent (alcohol), gram-negative bacteria loose the color from the dye using the gram staining technique, when the thin cell walls, with less peptidoglycan, allow the solvent to penetrate and remove the color.
** Gram-positive bacteria remain purple after gram-staining because of their thick cell walls with large amounts of peptidoglycan.
107 Campbell, N., Reece, J.,(2002), p.528-529.
108 Hammond, S. M., Lambert, P. A., (1978), p.37-38.
109 Campbell, N., Reece, J.,(2002), p.81ff.
110 Hammond, S. M., Lambert, P. A., (1978), p.37-38.
111 Campbell, N., Reece, J.,(2002), p.81ff.

helix are separated, exposing the nucleotides on both chains. Free nucleotides attach to the template stands and are linked together by DNA polymerase. mRNA synthesis is similar to DNA replication; one DNA strand is used as a template and a RNA polymerase links together the matching ribonucleotides.[112,113]

Bacterial protein synthesis

Proteins are chains of amino acids held together by peptide bonds and different combinations of amino acids provide the protein with specific functions e.g. maintaining the shape of the cell membrane, controlling the metabolic activity. The ribosome consists of protein and ribosomal RNA divided into two subunits, 30S and 50S, and is the organelle that carries out the protein synthesis. All information needed for protein synthesis is encoded in the DNA and the transcription, the copying, of a specific part of the DNA which encodes for a certain protein onto a strand of messenger RNA, is first carried out in the process of synthesis. The mRNA attaches to the ribosome and transfer RNA, with a peptide chain at one end and a specific anticodon on the other, and binds to the complementary bases of the mRNA with hydrogen bonds. tRNA keeps adding peptides to the chain on the ribosome releasing a newly synthesized polypeptide chain with peptide bonds, a protein, when the correct number of amino acids has been assembled. This process is called translation.[114,115]

Bacterial cell metabolism

Metabolism is the sum of all chemical reactions and is responsible for managing the energy resources in the cell. Energy is released when complex molecules are broken down to simpler compounds and such degradative processes are called catabolic pathways. Anabolic pathways are, in opposite, consuming energy in order to build complex molecules from simpler ones.[116]

Folic acid is essential for bacterial growth. Prokaryotic cells must synthesize folates while humans and other eukaryotes can obtain folates from the environment. Folates, molecules composed of pterin, para-aminobenzoic acid (*p*ABA) and glutamate residues, are involved in many key metabolic functions in the bacterial cell e.g. the biosynthesis of nucleic acids and amino acids[117].

112 Campbell, N., Reece, J.,(2002), p.292-315.
113 Bell, S. D., (2006).
114 Ramakrishnan, V., (2002).
115 Hammond, S. M., Lambert, P. A., (1978), p.48-49.
116 Campbell, N., Reece, J.,(2002), p.87-88.
117 Bosson, G., (2003).

B. Self-medication with Antimicrobial Drugs in Europe

Actual use of systemic antimicrobial drugs in the last 12 months and at-risk self-medication in 19 European countries

Country (region in country)	Rate per 1,000 respondents (95% confidence interval)				
	Actual self-medication	Prescribed use	Intended self-medication	Storage* (conservative estimate)	Storage† (maximum estimate)
Countries with response rate ≥40%					
Northern and western					
The Netherlands (Twente)	1 (0.2–4)	152 (134–170)	85 (71–101)	10 (6–17)	36 (28–46)
Sweden (Vastmanland)	4 (0.9–12)	135 (109–161)	118 (94–143)	14 (7–26)	43 (29–60)
Denmark (Funen, Aarhus, Copenhagen‡)	7 (4–12)	172 (154–189)	132 (116–147)	42 (33–52)	84 (72–97)
Luxemburg (whole country)	9 (3–19)	288 (252–324)	83 (62–107)	90 (69–114)	132 (106–158)
Belgium (East Flanders, Flemish Brabant)	9 (5–15)	222 (201–242)	80 (67–95)	71 (59–84)	123 (107–138)
Southern					
Malta (whole country)	56 (38–79)	422 (380–465)	228 (192–264)	156 (125–186)	269 (232–306)
Eastern					
Czech Republic (Hradec Krlov)	7 (3–13)	253 (228–279)	179 (156–201)	45 (33–58)	64 (51–80)
Slovakia (Middle Slovakia region)	42 (27–63)	569 (527–612)	324 (284–365)	192 (159–225)	302 (263–340)
Romania (Dolj)	198 (160–235)	307 (263–351)	431 (383–478)	200 (162–238)	321 (277–365)
Countries with response rate <40%§					
Northern and western					52 (33–77)
Austria (Upper Austria)	9 (2–23)	159 (124–195)	73 (49–103)	34 (19–55)	52 (33–77)
United Kingdom (Nottinghamshire)	12 (5–23)	221 (189–254)	166 (137–195)	33 (21–49)	74 (56–97)
Ireland (Cork)	14 (7–25)	353 (320–386)	150 (125–176)	29 (19–43)	100 (80–123)
Southern					
Israel (Northern Israel)	15 (6–31)	330 (287–374)	187 (150–223)	120 (91–149)	236 (197–274)
Italy (Abruzzo)	62 (33–103)	512 (444–580)	243 (185–301)	379 (314–445)	569 (502–636)
Spain (autonomous community of Madrid)	152 (103–201)	315 (251–379)	314 (249–380)	260 (200–320)	500 (431–569)
Eastern					
Slovenia (Ljubljana region)	17 (10–26)	293 (266–320)	280 (253–307)	119 (100–137)	183 (160–205)
Croatia (Zagreb county)	31 (19–48)	439 (399–478)	205 (172–237)	130 (103–156)	212 (179–244)
Poland (Pomorskie)	33 (23–47)	199 (172–225)	115 (94–136)	69 (53–87)	137 (115–160)
Lithuania (Klaipeda, Rietavas)	210 (181–239)	275 (243–308)	449 (412–486)	177 (149–204)	333 (299–367)

*Included only those respondents who stored antimicrobial drugs and had not taken the same antimicrobial drugs for a prescribed course in the previous 12 months.
†Including all respondents who stored antimicrobial drugs.
‡Although Copenhagen has population >750,000, both self-medication and prescribed use of antimicrobial drugs were not significantly different between the sample of Copenhagen and sample of the other 2 Danish counties (χ^2 tests).
§The rates for these countries should be interpreted as first rough estimates.

C. Questionnaire

Hello,

I'm working on a project on antibiotic use and resistance at Uppsala University, Sweden. Antibiotics are rapidly loosing their effect and especially our misuse is one of the factors promoting the resistance to grow. The increasing resistance to antibiotics among many bacteria causing diseases is an important issue, as the growing resistance will seriously decrease the possibility to treat bacterial infections effectively. One important example of this is pneumonia where antibiotic resistance will cause severe difficulties in treatment and cure with increased fatalities as a result.

My name is Ann-Sofie Magnusson and I am a student working on a project initiated by ReAct - Action on Antibiotic Resistance (www.reactgroup.org), a global coalition with its coordinating node at Uppsala University. The project is supervised by Cecilia Stålsby Lundborg (Assoc Prof, PhD, MscPharm) and Otto Cars (Prof., MD, PhD). ReActs vision is that "current and future generations will have access to effective prevention and treatment of bacterial infections as part of their right to health" (see attached file for more information about the mission of ReAct). The purpose of this project is to map organizations worldwide, which are new to questions related to antibiotic resistance but are working in areas where the resistance could be a relevant issue (e.g. health and environment, rational use of medicine), and also to examine how extensive the interest is in questions concerning antibiotic resistance.

The reason why I am contacting you is that we would like to learn more about your organization and hear your thoughts and opinions on the problem of antibiotic resistance. It would be very helpful and valuable if you could answer a few questions (see below) on this subject, and if I could contact you again later if I need any supplementary information. If you would like to participate, please answer the questions below directly in a reply-mail to me. If applicable, please give a contact phone number for follow-up questions if needed.
Your phone number:

If you for some reason do not want to participate please send information on that so that I will not unnecessarily bother you with reminders.

Please respond as soon as possible, preferably before January X, 2007.

Thank you!

Best wishes Ann-Sofie Magnusson

To answer question 1a-1b, 3a-3d and 6a: Please write your answer in the space below each question.

To answer question 2, 4a-4c, 5, 6b: Please mark your alternative/alternatives with an X within the square brackets ([X]). For descriptions in 4a-4c and in 6b, please write your answers in the spaces below each question.

1a. Please describe briefly your organizations main focuses and goals, and where your organization operates.

b. What are your main working areas?

2. Have you heard of antibiotic resistance?
Yes [ ]
No [ ]

3. From the experience of working with your members/member organizations, what would you say are the main issues concerning...

(a) the use of antibiotics?

(b) the access to antibiotics?

(c) side effects of antibiotics?

(d) other aspects related to antibiotics?

4a. Have you previously worked with questions related to antibiotics?
No [ ]
Yes, in the last year (2006) [ ]
Yes, before 2006 [ ]
Please describe your work.

b. Are you currently working with questions related to antibiotics?
No [ ]
Yes [ ]
Please describe your work.

c. Are you interested in working with questions related to antibiotics in the future?
No [ ]
Yes [ ]
Please describe your interest.

5. Do you think it's important to raise the awareness of antibiotic resistance with doctors, other health professionals, authorities and consumers in your area?
With doctors; Yes [ ] No [ ]
With health professionals; Yes [ ], No [ ]
With consumers; Yes [ ], No [ ]

6a. How do you think awareness of this kind of issue can be raised?

b. Would your organization be willing to participate in such awareness raising?
No [ ]
Yes [ ]
If yes, how?

D. Mission and vision of ReAct

This document can be found at www.reactgroup.org

React - Action on Antibiotic Resistance - is an international coalition of individuals, organizations and networks committed to combat antibiotic resistance as a global threat to health.

Vision
Current and future generations will have access to effective prevention and treatment of bacterial infections as part of their right to health.

Mission
React seeks profound changes in understanding and responses to infection and antibiotic resistance through a social movement which engages civil society, community and consumer organizations, health policy reformers and those individuals, networks or institutions that generate and analyze health-related knowledge. React will catalyze and co-ordinate action in ways most likely to make these changes. In striving for its vision, React is committed to change four fundamental dynamics underlying the ability to prevent and treat infection. React believes: That antibiotics be used appropriately in humans, animal and plants - their use reduced when of no benefit, and their correct and specific use increased when needed;
That hospital and community infectious diseases be prevented through improved infection control and better hygiene and nutrition;
That awareness is needed of ecological balance in all aspects of human life as part of a comprehensive and integral concept of health;
That the root causes and responses to antibiotic resistance are social, political and ecological as much as scientific and technical.

Strategies
React will mobilise attention to, resources for and collaboration to combat development and spread of antibiotic resistance around the world by: Stimulating, organizing and supporting political, professional and community action; Making the burden of antibiotic resistance more transparent to policy makers and the public, and advocating that governments set up effective systems to reduce it; Encouraging and supporting processes of consumer and health care worker empowerment; Building alliances with groups across various sectors, and linking to campaigns with related and shared goals, e.g. those dealing at global and country level with HIV/AIDS, tuberculosis, malaria as well as initiatives on patient safety and rational use of medicines; Promoting strategies for the development of new antibacterials and complementary technologies, including diagnostics and vaccines, that might reduce reliance on antibiotics; Promoting new ways of approaching the problem of antibiotic resistance including a new understanding of the fundamental relationships, both beneficial and harmful, among humans, microbes, other living beings, infection, medicines and lifestyle.

Values
React strives to base its arguments on the highest quality of science.
Maintains due respect for traditional and indigenous medical systems that may have the potential to help prevent antibiotic resistance.
Stands against the use of microbes as agents of bioterrorism and strongly opposes efforts to develop antibiotic resistant strains towards such ends.
Works towards equitable health care access for all people in its advocacy for prevention and treatment of infectious disease.
Recognizes the unequal burden of antibiotic resistance on the poor and disadvantaged, especially women and children and supports their advocacy for health.

Respects the right of people in all countries to informed consent, ethical standards for clinical trials, and high standards of research conduct, and requires partners joining its work to respect this principle.
Functions in a transparent manner to seek, disclose and avoid conflict of interest – perceived or real- in its own activities to ensure the credibility of its policy voice.

E. Results from the questionnaire

Have you previously worked with questions related to antibiotics?

Answer alternative	*Number of org.*	*Percentage*
No	18	33.3%
Yes, in the last year (2006)	7	13.0%
Yes, before 2006	17	31.5%
Yes, both before 2006, and in the last year (2006)	8	14.8%
Blank	4	7.4%

Are you currently working with questions related to antibiotics?

Answer alternative	*Number of org.*	*Percentage*
No	29	53.7%
Yes	23	42.6%
Blank	2	3.7%

Are you interested in working with questions related to antibiotics in the future?

Answer alternative	*Number of org.*	*Percentage*
No	1	1.9%
Yes	50	92.6%
Blank	3	5.6%

F. Responding organizations and networks

Africa

Association des Consommateurs du Mali (ASCOMA)
Area/Location: Mail
Contact: Salimata Diarra
ascoma70@yahoo.fr

Consumers Association of Ghana (CAG)
Area/Location: Ghana
Contact: Frederick Aye
consumersghana@yahoo.com

Consumer Protection Council (Nigeria)
www.commerceng.org
Area/Location: Nigeria
Contact: Mopelola O. Akeju
lolakeju@yahoo.com

Women's Health Action Research Centre (WHARC)
http://wharc.freehosting.net
Area/Location: Nigeria
Contact: F. O. Okonofua
wharc@hyperia.com

Zambia Consumers Association (ZACA)
Area/Location: Zambia
Contact: Muyunda Ililonga
zaca@zamnet.zm

America

Center for Science in the Public Interest (CSPI)
www.cspinet.org
Area/Location: USA, Canada
Contact: Benjamin Cohen
bcohen@cspinet.org

Consumer Federation of America
www.consumerfed.org
Area/Location: USA
Contact: Chris Waldrop
cfa@consumerfed.org

Consumers Union of U.S. Inc.
www.consumersunion.org
Area/Location: USA
Contact: Carolyn Cairns
cairca@consumer.org
Food Animal Concerns Trust (FACT)

www.foodanimalconcernstrust.org
Area/Location: USA
Contact: Steven Roach
saroach@fact.cc

Health Action International (HAI) – Latin America
www.aislac.org
Area/Location: Latin America - Peru
Contact: Roberto Lopez
robertolopez@aislac.org

Institute for Agriculture and Trade Policy
www.iatp.org
Area/Location: USA
Contact: David Wallinga
dWallinga@iatp.org

Public Citizen's Health Research Group
www.citizen.org/hrg
Area/Location: USA
Contact: hrg1@citizen.org

Asia

Annamalai University
http://annamalaiuniversity.ac.in
Area/Location: India
Contact: Guru Prasad Mohanta
gpmohanta@hotmail.com

Armenian Public Health Union (APHU)
www.publichealth.am
Area/Location: Armenia
Contact: Margaryants Hovhannes
hmargaryants@armhealth.am

Citizen, Consumer and Civic Action Group (CAG)
www.cag.org.in
Area/Location: South India
Contact: Bharath Jairaj
Cag.india@gmail.com

Consumers Association of India
Area/Location: India
Contact: Nirmala Desikan
consumersassnofindia@vsnl.net

Consumers Association of Penang (CAP)
Area/Location: Malaysia
Contact: Kireen Marion
kireenmm@tm.net.my

Consumer Unity and Trust Society (CUTS)
www.cuts-international.org
Area/Location: India
Contact: Keya Ghosh
rdm@cuts.org

Department of Pharmacy, Kathmandu University
www.ku.edu.np/pharmacy
Area/Location: Dhulikhel, Nepal
Contact: Gulam Muhammad Khan
gmkhan@ku.edu.np

Drug Action Forum – Karnataka (DAF-K)
Area/Location: India
Contact: Gopal Dabade
drdabade@gmail.com

Federation of Consumer Organisations Tamilnadu & Pondicherry (FEDCOT)
www.fedcot.org
Area/Location: India
Contact: P. Durai Singam
fedcotdurai@yahoo.com

Federation of Malaysian Consumers Associations (FOMCA)
www.fomca.org.my
Area/Location: Malaysia
Contact: Cheah Chee Ho
cch@fomca.org.my

Health Action International – Asia Pacific
www.haiap.org
Area/Location: Asia Pacific
Contact: Prasadini Perera
prasadini@haiap.org

Health And Nutrition Development Society (HANDS)
www.hands.org.pk
Area/Location: Pakistan
Contact: Aslam Khan
aslam.khan@hands.org.pk

Locost
www.locostindia.com
Area/Location: India
Contact: Srinivasan
sahajbrc@icenet.co.in

The Network for Consumer Protection in Pakistan
www.thenetwork.org.pk
Area/Location: Pakistan
Contact: Ayyaz Kiani
ayyaz@thenetwork.org.pk

Vietnam Standards and Consumers Association (VINASTAS)
Area/Location: Vietnam
Contact: Do Gia Phan
vinastas@fpt.vn

Voluntary Health Association of India (VHAI)
www.vhai.org
Area/Location: India
Contact: Pramesh Bhatnagar
pramesh9@gmail.com

Australia

CHOICE
www.choice.com.au
Area/Location: Australia
Contact: Clare Hughes
chughes@choice.com.au
Viola Korczak
vkorczak@choice.com.au

Europe

Associação Portuguesa de Direito do Consumo
www.apdconsumo.pt/
Area/Location: Portugal
Contact: Ana Paula Frota
apdc.cedc@mail.telepac.pt

Association of Consumer Rights Protection
Area/Location: Turkey
Contact: Taylan Sevim
taylanise@hotmail.com

Association of Polish Consumers (APC)
www.skp.pl/eng
Area/Location: Poland
Contact: Aleksandra Wesolowska
consumer@skp.pl

Association of Slovak Consumers
www.zss.sk
Area/Location: Slovakia
Contact: Miroslav Tulák
tkidaho@stonline.sk
zss@zss.sk

Belgian National Homeopathic Union
www.homeopathy.be
Area/Location: Belgium
Contact: Michel Van Wassenhoven
michelvw@homeopathy.be

Bulgarian National Consumer Association
www.bnap.org/en
Area/Location: Bulgaria
Contact: Asen Nenov
asen.nenov@bnap.org

Consumers Defence Association of the Czech Republic (SOS)
www.spotrebitele.info
Area/Location: Czech Republic
Contact: David Šmejkal
smejkal@spotrebitele.info

Dag Hammarskjöld Foundation
www.dhf.uu.se
Area/Location: Sweden
Contact: Kajsa Övergaard
Kajsa.overgaard@dhf.uu.se

European Research into Consumer Affairs (ERICA)
www.net-consumers.org
Area/Location: Europe
Contact: Chris Andrew
chris.andrew@net-consumers.org

Food Ethics Council
www.foodethicscouncil.org
Area/Location: UK
Contact: Tom MacMillan
tom@foodethicscouncil.org

Global Alliance for TB Drug Development
www.tballiance.org
Area/Location: Netherlands
Contact: Nina Schwalbe
nina.schwalbe@tballiance.org

Global Health Watch
www.ghwatch.org
Area/Location: International
Contact: Bridget Lloyd
bridget@hst.org.za

Green Doctors – ISDE Ukraine
Area/Location: Ukraine
Contact: Lew Gerbilsky
Lew.gerbilsky@t-online.de

Hea**lth Action International (HAI) – Europe**
www.haiweb.org
Area/Location: Europe
Contact: Colleen Daniels
colleen@haiweb.org
Teresa Alves
teresa@haiweb.org

Health Development Promotional and Educational Center (CEPRO-MED)
Area/Location: Serbia and Montenegro
Contact: Nikolic Branka
N_branka@eunet.yu

Kentro Prostasias Katanaloton (KEPKA)
www.kepka.org
Area/Location: Greece
Contact: Nikolaos Tsemperlidis
Evangelia Kekeleki
consumers@kepka.org

Konsumentföreningen Stockholm
www.konsumentforeningenstockholm.se
Area/Location: Sweden
Contact: Louise Ungerth
Louise.u@konsumentforeningenstockholm.se

Neytendasamtökin (NS)
www.ns.is
Area/Location: Iceland
Contact: Brynhildur Pétursdóttir
brynhildur@ns.is

Organización de Consumidores y Usuarios
www.ocu.org
Area/Location: Spain
Contact: David Miguel Ortega
dortega@ocu.org

Pharmaceutical Group of the European Union (PGEU)
www.pgeu.org
Area/Location: Europe
Contact: Giovanni Mancarella
g.mancarella@pgeu.eu

Sustain
www.sustainweb.org
Area/Location: UK
Contact: Jeanette Longfield
jeanette@sustainweb.org
sustain@sustainweb.org

Sveriges Konsumentråd
www.sverigeskonsumentrad.se
Area/Location: Sweden
Contact: Jens Henriksson
jens.henriksson@sverigeskonsumentrad.se

Test-Achats/Test-Aankoop Belgium
www.test-achats.be, www.test-aankoop.be
Area/Location: Belgium
Contact: Maurice Vanbellinghen
mvanbellinghen@test-aankoop.be

The Consumer Council of Norway
www.forbrukerradet.no
Area/Location: Norway
Contact: Line Andersen
line.andersen@forbrukerradet.no

Union Luxembourgeoise des Consommateurs
www.ulc.lu
Area/Location: Luxembourg
Contact: Jean Feyereisen
ulcegc@pt.lu jf@ulc.lu

Verbraucherzentrale Bundesverband (VZBV)
www.vzbv.de/go/
Area/Location: Germany
Contact: Jutta Jaksche
jaksche@vzbv.de

Verein für Konsumenteninformation (VKI)
www.konsument.at
Area/Location: Austria
Contact: Eva Matt
ematt@vki.or.at
Michael Wasicky
MWasicky@vki.or.at