Antibiotic Resistance in Salmonella enterica and the Role of Animal and Animal Food Control

A literature review of Europe and USA

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Abstract

Background: Salmonellosis is one of the major foodborne diseases with a high incidence and severity. Antibiotic resistance is a growing public health emergency since infections from resistant bacteria are more hard and costly to treat. Since the 1990, some strains of Salmonella became resistant to a range of antibiotics. Nowadays, multidrug resistance has become a critically important issue in public health. The risk development of antibiotic resistance in human and animal is one of the main reasons for control in animals.

Objective: The main objective is to chart the relationship between antibiotic resistance of Salmonella enterica and control of Salmonella in animals and animals' food. The second objective is to describe the situation regarding Salmonella enterica control and antibiotic resistance in selected countries in Europe and USA and to analyse which component regarding the control programmes are crucial for a reduction in antibiotic resistance.

Methods: A literature search was performed in the field regarding antibiotic resistance of Salmonella with focus on the situation in Europe mainly Sweden and Denmark, and USA.

Main finding: The study shows strong inverse relationship between antibiotic resistance of Salmonella enterica and control of these bacteria in animals and animals' food. This study shows the prevalence of Salmonella enterica and antibiotic resistance is high in countries with low control like as Denmark and USA. The existing literature on Salmonella resistance sheds light on the fact that, Sweden is the most successful country in Europe in controlling Salmonella and antibiotic resistance. This is a consequence of efficient policy towards controlling the antibiotic resistance by effective management and regular prevention programs and controlling different levels like feed, food-producing, animals and humans also decrease in the consumption of antibiotic in animals and collaboration of different organization in Sweden.

Conclusion: Control of Salmonella in animals, animals' food, food and human are the important keys for controlling of antibiotic resistance. Low consumption of antibiotics in animals and humans; the low prevalence of Salmonella due to strict control programs result in a relatively low frequency of antibiotic resistance. The success of any disease control program lies in the effectiveness and intensity of cooperation. The degree of better communication between veterinary organizations and health care providers is important in order to exchange the knowledge and relevant information. In order to have control over spread of salmonellosis and to target antibiotic resistance, international collaboration is needed.
Abbreviations and Acronyms

AMR: Antimicrobial Resistance

CDC: United States Centers for Disease Control and Prevention

DANMAP: Danish Integrated Antimicrobial Resistance Monitoring and Research Program

ECDC: European Center of Disease Control

EFSA: European Food Safety Authority

ESBL: Extended Spectrum Beta Lactamase

EU: European Union

FAO: Food Agriculture Organization of the United Nation

FDA: Food and Drug Administration

FVE: Federation of Veterinary of Europe

GDP: Gross Domestic Product

HACCP: Hazard Analysis Critical Control Points

HGT: Horizontal Gene Transfer

OIE: World Organization of Animal Health

MDR: Multiple Drug Resistance

MIC: Minimum Inhibitory Concentration

MLVA: Multiple-Locus Variable amount of tandem repeats Analysis

QRA: Quantitative Risk Assessment

RASFF: Rapid Alert System for Food and Feed

SBA: Swedish Board of Agriculture
SMI: Swedish Institute for Infectious Disease Control

Strama: Swedish Strategic Program against Antibiotic Resistance

SVA: Swedish National Veterinary Institute

SVARM: Swedish Veterinary Antimicrobial Resistance Monitoring

VREF: Vancomycin-resistant Enterococcus Faecalis

WHO: World Health Organization of the United Nation
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1. Introduction

Food safety is a major public health issue (1). Governmental agencies are trying to improve food safety all over the world. The universal rate of foodborne disease is difficult to estimate but in 2005, around 1.8 million people died from diarrheal diseases. A large percentage of these cases can be certified to contamination of food and drinking water (1). In addition diarrhea is a major reason of malnutrition in infants and young children (1). In USA about 76 million cases of foodborne diseases resulted in 325,000 hospitalizations and 5,000 deaths are calculated to happen each year (1).

Antibiotic resistant of bacteria is a growing public health emergency since infections from resistant bacteria are more hard and costly to treat (2). Since the 1990, some strains of Salmonella became resistant to a range of antibiotics. The resistance is caused by the use of antibiotics in humans and animals husbandry. Nowadays, multidrug resistance (MDR) has become a critically important issue in public health (2).

Salmonellosis imposes a significant cost to society in many countries but just few countries report the data on economic cost of the disease (2). It is estimated that 1.4 million non-typhoid Salmonella infections resulted in 168,000 visits to physicians whereas 15000 hospitalizations and 580 deaths occur in the United States annually (2). The estimated cost per case of human salmonellosis was approximately US$ 1,938 and total cost was close to US$ 3 billion annually in the United States in 2010 (5).

In 2001, the estimated cost of nontyphoidal salmonellosis in Denmark was US$ 15.5 million which was 0.01% of Gross domestic product (GDP). The annual estimated cost of this control program in Denmark is US$ 14.1 million which resulted in reducing the Danish public expenses to US$ 25.5 million annually. Unfortunately, there is not enough evidence regarding the cost of foodborne disease in developing countries (2).
1.1 Salmonellosis

Salmonellosis is one of the most common public health problems in many countries. Outbreaks of salmonellosis are seen in eggs, poultry and other meats, raw milk and chocolate (1). In recent years Salmonellosis has increased considerably both in incidence and severity. Efforts to prevent and control this disease are important because of many reported human cases and thousands of deaths every year. In European countries, almost 192703 human cases of salmonellosis were reported in 2004. This shows the magnitude of the problem especially since many cases of salmonellosis are not reported. Salmonella Enteriditis and Salmonella Typhimurium are the most important serovars those are transmitted from animals to humans (3). Salmonella Enteriditis has become the most common cause of salmonellosis in humans. It is usually transferred by contaminated food of animal sources (meat, poultry, eggs, milk) or vegetables contaminated by manure and water. Some of the precautionary measures include those foods which should be correctly cooked (mainly chicken, egg products and foods contain unpasteurized milk), and water should be boiled. Salmonella infection has spread over the world, through live animals and international trade in animal feed. The control of Salmonella is thus a critical challenge confronted by veterinary services and producers who want to produce safe food of animal origin (3). The clinical symptoms are acute like, fever, abdominal pain, and diarrhea and vomiting. Sometimes complications may arise like secondary septicemia and reactive arthritis. In young population and in the elderly, these symptoms become severe and life-threatening. Studies show that, the source of disease in more than 80% of all cases occurring are individual basis rather than as outbreak (3).

1.2 Microbiology of Salmonella

Salmonella is one of the members of Entrobacteriaceae family. They are gram-negative, oxidize negative, non-spore forming, facultative anaerobic, rod shape and motile by peritrichous flagella. The cell wall of Salmonella compounds the structure of lipids, polysaccharides, protein and lipoproteins. The lipopolysaccharide portion of the cell wall and lipid A is endotoxin. Endotoxin is responsible for the biological effects. The common
center monosaccharides and polysaccharides of endotoxin are also called somatic O antigens. Salmonella has about 60 of O antigens that are nominated by numbers. Furthermore, there are some unlike flagella (H) antigens that they are recognized by numbers and letters. Based on these somatic antigens, Salmonella may be divided into groups which are using specific antisera. By using somatic and flagella agglutination reactions almost 2500 (2483 in the year 2000 REF) serovars have been recognized. The Kauffman-White classification shows that majority of the Salmonella involved in human disease belong to groups A, B, C, C2, D and E. Salmonella Typhi hold a capsular antigen called the virulence antigen which envelops the cell wall. Salmonella grows readily on blood agar, MacConkey agar or Eosin-Methylene blue. Bismuth Sulfate agar or desoxycholate agar should be used for the identification of Salmonella and it (Salmonella) ferments glucose and mannose but not lactose or sucrose (6).

1.2.1 Virulence Factors

Despite significant research, knowledge about the survival of Salmonella, how the bacterium adheres and penetrates to the host and the cause of disease is still not well understood. The cause of disease is dependent on several virulence determinants, this includes genes involved in nutrient uptake, stress response and renovate of cell damage. Other virulence factors of Salmonella are Endotoxins, Exotoxins, Fimbriae and Flagellae. These genes are particular for Salmonella, encode adaptations to overcome defense mechanisms and are true virulence determinants. The genetic control of Salmonella is not fully identified (3).

Salmonella Dublin, Abortusovis, Enteritidis, Choleraesuis, Typhimurium and Gallinarum/ Pullorum are six serovars of Salmonella. All these serovars (plasmids) have the virulence (spv) locus. This locus has five genes. There is not enough information regarding the exact function of the encoded proteins. Gene expression happens under situation like low pH, and nutrients supply (3).
1.3 Salmonellosis in Human

Nontyphoid Salmonellosis is usually recorded as a localized enterocolitis. The incubation phase ranges from five hours to seven days but medical signs regularly begin 12 -36 hours after intake of infected food. Shorter incubation periods are usually related to higher doses of the pathogen or highly at risk people. Medical signs include diarrhea, nausea, abdominal pain, fever, chills, vomiting, prostration, anorexia, headache and malaise may also occur. The disease period is most often two to seven days. Systemic infections sometimes happen and frequently involve the very young, old or the immune-compromised hosts. A few numbers of cases may lead to death. The patients have a large numbers of Salmonella spp at the start of disease. Some of the patients become carriers but others have quality to excrete Salmonella after 3 months. Nontyphoid salmonellosis can cause chronic diseases with localized infections in particular organs, reactive arthritis, neurological and neuromuscular diseases (3).

1.4 Salmonellosis in Animals

Salmonellosis in animals is divided into different subtitles. The main serovars of Salmonella that develop disease in specific animal are: Salmonella Abortusovis in sheep; Choleraesuis in pigs; Gallinarum in poultry; Abortus Equi in horses and Dublin in cattle. These serovars mostly cause abortions or acute gastroenteritis in their animal. The main serovars of Salmonella that develop disease in multi animal and human hosts include S. Typhimurium, S. Enteritidis, S. Hadar and S. Infantis. In animal hosts, these serovars cause acute septicemia, enteritis or chronic enteritis. The animals can also have a subclinical disease with few symptoms or become a transitory or persistent carrier (3).

In summary, in most food of animal, Salmonella frequently create a clinically unapparent infection with various periods that have importance in zoonosis. Serovars that are usually non-pathogenic may also cause sickness in animal species under different stress conditions that are later used as meat. Sweden, Finland and Norway have achieved practically animal products without Salmonella as the consequence of an intervention policy, which proposed zero tolerance for Salmonella (3).
1.5 Antibiotic Resistance

1.5.1 Definition

Antibiotic resistance in microorganisms is either genetically inherent or the result of the microorganism being exposed to antibiotic. Most of the antibiotic resistance has emerged as a result of mutation or through transfer of genetic material between microorganisms. A broad variety of biochemical and physiological mechanisms are responsible for the development of resistance. Recent studies of almost 400 different bacteria have demonstrated about 20,000 possible resistance genes (r genes) (8).

1.5.2 Mechanisms of Resistance

The mechanism of antibiotic resistance can be identified in four types:

1. Antibiotic modification; bacterial enzymes like Betalactamase alter the structure of the antibiotic and thereby render the antibiotic in effectiveness. It’s a mechanism in gram positive and negative bacteria species to Betalaktam antibiotics like Cephalosporin. The effect of Betalactamase can be to some extent inhibited by clavulanic acid.

2. Preventing the antibiotic from entering the bacterial cell or pumping it out quicker than it floods in. This mechanism is shown in imipenem resistance in Pseudomonas auruginosa and with tetracycline resistance.

3. Antibiotic is unable to inhibit the activity of the target structure in the bacteria because of structural changes in the bacterial molecule. This is seen in inherent resistance to cephalosporin in Enterococci and in low resistance to penicillin in Streptococcus pneumoni.

4. The bacteria produce an alternative target like an enzyme that is resistant to inhibition by the antibiotic while continuing to produce the original sensitive target. This allows the bacteria to survive in the face of selection. This “bypass” is seen in methicillin resistant Staphylococcus aureus (7).
1.5.3 Natural Resistance

Intrinsic resistance is the survival genes in bacterial genomes that could create a resistance phenotype (8). Differences in environmental factors could be responsible in existence of numerous number and sorts of resistance (8). Antibiotic usage by human and releasing to the environment can promote antibiotic resistance in every place. Antibiotics are used as growth support for animal, therapeutic agent for humans, aquacultures, pets, pest control in agriculture, biocides in toiletries, hand care, culture sterility, cloning and industry (8). Genetic studies showed that wastewater and plants are reservoirs of antibiotic resistance (8).

1.5.4 Mutation

Resistance in bacteria could be inherent. This can happen by mutation or acquirement of new DNA. Mutation is spontaneous and transfer by plasmids or bacteriophages (7). Genetic mutation is the primary cause of antibiotic resistance. Antibiotic resistant is created from different ways, such as antibiotic usage both in medical and veterinary medicine that lead to distribution of bacterial resistance genes through other bacteria (9).

1.5.4.1 Examples of Antibiotic Resistance through Mutation

Some of bacteria have the ability to produce specific antibodies that are resistant to an extended Spectrum Beta Lactamase (ESBLs). The common place for these bacteria is lumen. These bacteria are expanded among patients and in hospitals. These groups of bacteria can then be transferred to other people by unwashed hands specially after using toilet (8).

The genes of B-lactamase enzymes are mainly global in circulation; random mutation of the genes encoding and the enzymes have increase to customized catalysts with ever more complete spectra of resistance. Another general family of DNA-binding proteins Gyrase inhibitors (Qnr) is answerable for low levels of quinolone resistance (8).
1.5.5 Gene Transfer

Genes can be transferred between bacteria in a horizontal way through conjugation, transduction and transformation. Transfer of genes can happen in the intestinal tracts of animals and human. Thus genes of antibiotic resistance can be shared. Most of antibiotic resistance genes reside on plasmids with self replicating circular pieces of DNA that make the transfer easier. If a bacteria have several resistance genes, it is called multi-resistant or a superbug or super bacterium. The name superbug refers to microbes with high levels of resistance to antibiotic. Some super resistant strains have high virulence and enhanced transmissibility. Certain antibiotic are associated with higher levels of development of superbugs (8).

It is proposed that soil microbes are reservoirs for antibiotic resistance genes that can transfer to other microbes (9). Stress increases the prevalence of resistance and the skills of bacteria to obtain these genes that may be absorb by the similar genetic elements in the bacterium that receive the resistant gene (9). The efflux systems can force offending compounds, like as antibiotics out of the cell and can produce a wide range of resistance (9). In some cases, the resistance genes can also import unknown advantages beyond those associated with the advantages selected under antibiotic use (12).

1.5.6 Development of Resistance

Antibiotic resistance is a global problem in public health and is growing around the world. Antibiotics have been used for 70 years but during the last decade some treatments have become ineffective and this may lead to spread of some infections in the future. Antimicrobial resistance (AMR) is created by use of antibiotics in a wrong way and develops when a microorganism have mutated or acquired inappropriate use of antibiotics in human and veterinary medicine leads to higher frequencies of AMR (11).

Antibiotics are often used in animals. Transfer to human’s food of these antibiotics can affect the safety of the meat, milk, and eggs produced and can be the source of superbugs. The resistant bacteria in animals can transfer to humans by three pathways, consumption of meat or other food, direct contact with animals or through the
AMR decrease the effectiveness of treatment and, the duration of infections can become longer which increases the risk of spread of the resistance to other microorganisms (11).

Resistance causes more expensive therapies and longer duration of sickness so antibiotic treatment becomes a higher financial burden to families and societies. AMR can compromise successful organ transplantation, cancer chemotherapy and major surgery (11).

The type, safety and efficacy of antibiotics used for animals are important and should be checked by performing field trials (12). There is another important issue is the pharmacokinetics of drugs such as; bioavailability, tissue distribution, half-life and tissue kinetics. It is better to use antibiotic with a narrow spectrum because of less risk of resistance. Correct dose and duration of antibiotic treatment is very important,
especially to avoid sub-therapeutic treatment as these are the factors that prevent multiple antibiotic resistances (12).

The most reason of antibiotic resistance in animal is antibiotic exposure. Other important factors include the population of the micro-organisms; pre-exposure prevalence of resistance genes; the fitness of the selected population of micro-organisms in competition with other unexposed micro-organisms present in the environment (12).

1.6 Epidemiology of Salmonella

Salmonella can stay alive for long times in the environment even if no important growth occurs. Infections in wild fauna like as rodents are usually secondary to the illness of farm animals although it can continue the infection cycles. The control of Salmonella is required to decrease the number of organisms that are discharged into the environment. Water and soil are also a part of the epidemiological cycle and can transfer bacteria to vegetables and herbs. The most high risk food categories which cause salmonellosis are raw or undercooked meat, eggs and products containing raw eggs, unpasteurized milk, and juices (3). Water, food which is contaminated with feces and an asymptomatic human carrier can be reservoir for Salmonella (13).

1.6.1. Transmission

Salmonella is mostly transferred to animals, food and environment (water, crops) by fecal shedding. Fecal or intestinal contagion of carcasses is the main resource of human foodborne infections. It is the exception when pathogen is directly transmitted into the food product, such as S. Enteritidis into eggs and sometimes other serovars into milk. Humans excrete the bacteria as animals do. Excreted bacteria infect other animals on the farm and can transmit to rodents and other wild fauna live near humans or domestic animals (1).
Trade of live animals is a way of transferring of Salmonella within and between countries. In Europe, S. Typhimurium is usually seen as a result of trade in calves and parent and grandparent flocks in poultry production. Also Trade in infected animal feed products and non-heat-treated animal products have considerably contributed to the spread of Salmonella. Salmonella is also spread between countries by humans as a result of food-borne infections. Finland, Norway and Sweden have a low prevalence of domestic Salmonellosis and up to 80% of human cases are attributed to visits abroad (1). The situation of countries such as Denmark and the Netherlands are in contrast (Figs 2 and 3).

**Figure 2:** Estimated contribution of travel and farm animal and their products to Laboratory-confirmed human salmonellosis cases and estimated salmonellosis case in the general population of the Netherlands, 1995-2005 Source: reference 1
**Figure 3:** Estimated sources of 1,538 cases of human salmonellosis in Denmark, 2004

Source: reference 1

### 1.6.2 Salmonella in the world

Travelling to another country, farm animals and animal foodstuffs accounted for most human salmonellosis cases in Netherland in 2003 while most of the salmonellosis cases in Denmark in 2004 were related to travel, pork, chicken, and eggs. Salmonella enteritidis and Salmonella typhimurium are the most common Salmonella serovars reported to infect humans in Denmark as in many European countries. Statistical data related to Denmark for year 2004 show that between 13.8 to 26.8% of all salmonellosis is related to non-heat-treated meat (3).

The most common serovars reported in humans in United States are Salmonella typhimurium, enteritidis, Heidelberg, Newport and Javiana. Salmonella enteric shows inherent resistance to tetracycline and sulfisoxazole (15).
1.7 Control of Salmonella

In 1980, World Health Organization (WHO) formulated three steps of control of Salmonella which still involve valid planned approaches to risk mitigation:

- First step is the Food-Producing Animal Regulations (pre-harvest control).
- Second step is the hygiene improvements during the slaughtering and additional processing of the meat (harvest control).
- Third step is the final preparation of food by training and education of the food processing industries and consumers about good hygiene practices (post-harvest control).

Since any serovar is a possible risk to human health, prevention of food-borne salmonellosis should be directed at all serovars of Salmonella. Though, a Salmonella reduction plan which is limited to a few elected serovars could also have a protective effect on most other serovars because of similar way of transmission. When a plan is implemented, a surveillance program will be required to notify the frequency of zoonotic serovars. Without interventions in the early stages of food or animal production, there is a chance of wide spread infection that could result in epidemic proportions in a short time. Networking between producers is a useful way to prevent respiratory and enteric infections in pig production, and establish appropriate methods for limiting the risk of Salmonella (9).

One way of controlling Salmonella is by using antibiotic in animals for four purposes:

1) For healing the sick animals
2) For Metaphylaxis, treatment and prevent disease
3) Prophylactic, prevention in times of risk such as transportation or weaning
4) Growth encouragement to the progress supply and product

Using of antibiotic in human and animals lead to resistance and monitoring program is necessary also (9).
1.8 Treatment of Salmonella

Fluoroquinolones are usually regarded as the first line treatment of salmonellosis in adults. They are fairly inexpensive, well tolerated, good oral absorption and effective on the majority of Salmonella strains. Third-generation cephalosporin is used for children with severe infections. Chloramphenicol, Ampicillin and Trimethoprim-Sulfamethoxazole are infrequently used as alternatives but have either more side-effects. The MDR Salmonella strains with resistance to fluoroquinolone and Third-generation cephalosporin can still be treated with other antibiotics but they are generally more dangerous and expensive (2).

Control of antibiotic resistant Salmonella is most efficiently through the reduction the consumption antibiotic. Control of Animal feed, husbandry, hygiene in abattoir routinely, sanitation at all stages and food services are ways to minimize the need for antibiotic treatment(2).

1.9 Antibiotic Resistance in Salmonella

Exposure of micro flora to antibiotics may increase the number of resistant factors which can transfer resistance to pathogen bacteria (9).

There is a strong association between consumption of antibiotic and antibiotic resistance of Salmonella. It is evident-based with the B-lactamases. Horizontal gene transfer (HGT) has a main role in the progress and diffusion of the resistance to the B-lactam antibiotic among the enteric bacteria in both community and hospital level infections (8). Regular mutations in the genome of DNA create resistance to Fluoroquinolones and other antibiotics by transfer of DNA between bacterial strains. MDR is transferred through one coherent piece of DNA which is called plasmid (2).

There was no evidence of Salmonella resistance in human with consumption of Fluoroquinolones but with consumption of antibiotic in animal feed was observed and the rate of resistant in animal, food and human is quickly increased in several countries (2).
MDR strains of Salmonella have increased significantly in recent years. Some variants of Salmonella have acquired MDR as the genetic material of the organism and when antibiotic drugs are no longer used, resistance remains (2).

MDR Salmonella appears in reaction to antibiotic usage in animal feed. Consumption of antibiotics is a main reason of resistance but other factors also need to be considered. For example, some Salmonella serovars are more sensitive to develop resistance than others. In addition, incidence of Salmonella serovars in animal and humans are often seen. A recent example is the worldwide spread of a MDR Typhimurium phage type DT104 in animals and humans (2).

Recent studies showed the consequences of antibiotic resistant on human health. These consequences can be separated into two categories: first, the infections that may not have occurred and secondly, the high incidence of treatment failures and increase in the severity of disease (2).

Use of antibiotic agents in humans and animals affect all bacteria in the intestinal tract. People are using antibiotic drugs for unrelated reasons and have Salmonella in the intestinal tract are at risk of becoming Salmonella resistant to the antibiotic agent. This risk can be described as an attribute fraction (2).

In a recent study more than one million cases of Salmonella disease occurred each year in the United States, it is estimated the antibiotic resistance in Salmonella may cause additional 30,000 cases, 300 hospitalizations, and 10 deaths. Consumption of antibiotic in animals can lead to the transmission of resistant bacteria between animals, and spread to humans through food (2). High incidence of treatment failure and severity of infection can cause extended duration of sickness, increased rates of infection, hospitalizations and death (2).

1.9.1 Evidence of WHO

It is normal for resistant microorganisms spread as a result of irrational use of antibiotic and medicines because they provide favorable condition for them to survive. In cases of
patients that take poor quality antimicrobials, these resistant microorganisms are likely to emerge.

Principal factors that force Antibiotic multi resistance include:

- Insufficient observation and monitoring systems.
- Insufficient systems that make sure the supply of medicines is sufficient and have good quality.
- Undesirable consumption of medicines especially in animal husbandry practices.
- Poor prevention programs and control practices.
- Inaccurate diagnostic of methods, medicines and vaccines as well as inadequate reliable research and growth of new products (14).

1.9.2 WHO’s response to AMR

WHO is participated in response to AMR through: Policy making, surveillance, scientific support, knowledge generation and partnerships, including through programs for disease prevention and control essential medicines quality, supply and rational use:

- Necessary medicines value, supply and coherent use.
- Patient security
- Laboratory quality guarantee

WHO has chosen struggle against antibiotic resistance as an important subject for World Health Day 2011. It is supposed, WHO recommends a six-point plan package to stop widening of antibiotic resistance for governments (14).
2. Objective

Main objective:

The main objective is to chart the relationship between antibiotic resistance of Salmonella enterica and control of Salmonella in animal and animal’s food.

Secondary objectives:

1- Describe the situation regarding Salmonella enterica control and antibiotic resistance in selected countries in Europe and USA.

2- Analyse which component regarding the control programmes that are crucial for a reduction in antibiotic resistance.

3. Methodology

3.1 Literature search

A literature search was performed in the field regarding antibiotic resistance of Salmonella with focus on the situation in Europe and USA. The scientific articles were searched through Pub Med. The author used three main terms: “Salmonella enterica”, “Antibiotic resistance” and “control”. These terms were combined with an “AND” between the terms. This gave 344 hits in Pub med.

The reports and fact sheets searched according selection criteria: Salmonella enterica, Antibiotic resistance of Salmonella enterica and control programs in animals and animal’s food from the following sources:

World Health Organization(WHO), World Organization of Animal Health(OIE), Food and Agriculture Organization of the United Nations (FAO), United States Center for Disease Control and Prevention (CDC), United State Center for Emerging Issues, Federation of Veterinary of Europe(FVE), Swedish National Veterinary Institute(SVA),
Swedish Veterinary Antibiotic Resistance Monitoring (SVARM), ELSEVIER, and Google Scholar.

3.2 Selection criteria

After getting 344 hits on the Pub Med, the author chose 36 out of them after reading all the abstracts. The selection criteria describes the situation regarding Salmonella enterica control, antibiotic resistance and control programs in animals and animal’s food in selected countries of Europe and USA. Among European countries most focus was paid on Sweden and Denmark. The articles or publications that those included in this study were from year 2000 up to 2012, all written in English.

4. Result

The result describes the situation regarding the control of Salmonella enterica and antibiotic resistance. I also tried to identify critical aspects of the control programs according to the WHO criteria and identify which of the programs that was most successful of selected countries in Europe (Sweden, Denmark) and USA. This study showed the prevalence of Salmonella enterica and highlights that antibiotic resistance is high in European countries and USA except Sweden. Sweden has a complete control program in different parts. These parts represent programs for feed industry, Swedish Poultry Meat Association, animals, pre-slaughter, hatcheries, food and human investigation. Sweden also has programs for controlling antimicrobial resistance in human and animals. Denmark on the other hand has Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP). This program was not successful because they didn’t check areas such as imported meat, ready food, and pet animals. The National Antibiotic Resistance Monitoring System (NARMS), The Foodborne Active Surveillance Network (Food Net) and National Food Safety Initiative (FSI) are organized in USA. But these programs focused more on how to decrease the Salmonella than control of antibiotic resistance so they were not successful in USA. Table 1 shows a summary of the articles and papers that are used in Results part.
Table 1: Summary of selected references

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<th>No.</th>
<th>No. of Reference</th>
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<th>Author</th>
<th>Study period</th>
<th>Aim of article</th>
<th>Design</th>
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<td>Surveillance of zoonotic and other animal disease agent in Sweden 2009</td>
<td>Bjorn Bengtsson 2010 Sweden</td>
<td>2009</td>
<td>Surveillance of zoonotic and other animal disease</td>
<td>Report</td>
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<td>3.</td>
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<td>Aaron M.lynne 2008 USA</td>
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<td>7.</td>
<td>23</td>
<td>Danish Integrated Antibiotic Resistance Monitoring and Resistance Program</td>
<td>Anette M. hammerum</td>
<td>1995-2006</td>
<td>Monitoring DANMAP</td>
<td>Review</td>
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<td>Monitoring Antibiotic resistance in Denmark</td>
<td>Flemming Bager</td>
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<td>Describe of design DANMAP</td>
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<td>An Outbreak of salmonella typhimurim infection in Denmark, Norway, Sweden, 2008</td>
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<td>11.</td>
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<td>Linda Tollefson</td>
<td>Not mentioned</td>
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<td>12.</td>
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<td>Evidence of an Association Between use of Anti-microbial agents in Food Animals and Anti-microbial Resistance among Bacteria Isolated from Humans and the human Health Consequences of Such resistance</td>
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<td>National Antibiotic Resistance Monitoring System (NARMS) program Review</td>
<td>Conducted by FDA</td>
<td>Not mentioned</td>
<td>Review of NARMS</td>
<td>Review</td>
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<td>Author/Institution</td>
<td>Year(s)</td>
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<tr>
<td>14</td>
<td>9</td>
<td>Antibiotic resistance in bacteria associated with food animal: a United States perspective of livestock production</td>
<td>Alan G. Mathew 2007 USA</td>
<td>Not mentioned</td>
<td>Review association between antibiotic resistance and food animal</td>
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<td>15</td>
<td>34</td>
<td>Distribution of multidrug-resistance human isolates of MDR-ACSSuT Salmonella Typhimurium and MR-AmpC Salmonella Newport in the United States</td>
<td>Sharon k. Greene 2008 USA</td>
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<td>Determined distribution of MDR S.Typhimurium, S. Newport</td>
<td>Cohort study</td>
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<td>Salmonella control in Sweden</td>
<td>The Swedish poultry meat association 2011 Sweden</td>
<td>Not mentioned</td>
<td>Monitoring program</td>
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<td>20</td>
<td>Importance of wild birds in the spread of Salmonella</td>
<td>Helena palmgren 2002 Sweden</td>
<td>1997-2000</td>
<td>Spread of Salmonella in Wild Birds</td>
<td>Dissertation</td>
</tr>
</tbody>
</table>
4.1 Europe

The study focuses some countries in Europe such as Sweden, Denmark and few other countries. It is interesting to note that Sweden is successful towards controlling antibiotic resistance and prevalence of Salmonella enterica between European countries. Also the study highlights success key factors for Sweden. Denmark was the first country which started the monitoring program of antibiotic consumption and antibiotic agent resistance in animal, foods and humans in Europe.

4.1.1 Sweden

This part shows some of the control programs of Salmonella, antibiotic resistance and also describes the situation regarding Salmonella enterica control and antibiotic resistance and shows the critical points in control programs in Sweden.

4.1.1.1 Salmonella Control in Feed

Sweden has control programs for animal’s food and human food. Still a numbers of cases are reported every year. The control program regarding feed of animals started in 1950 with an agreement between Swedish National Veterinary Institute (SVA) and the feed industry. It included the process of heat treatment of feed pellets to remove Salmonella. The Hazard analysis critical control points (HACCP) program started in 1993. Under this program, factories covered by Good Manufacturing Practice (GMP), take samples from their producing line weekly (5 samples of poultry products and 2 samples of other animals) and these are sent for analysis to SVA. Those samples which are Salmonella positive samples from imported feed are reported in the Rapid Alert System for Food and Feed (RASFF). Positive feed is regularly treated with organic acid like formic acid. If Salmonella is found in the producing line, the contaminated product must be cleaned
and disinfected also the factory and its’ environment must be disinfected. The results of Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) 2009 depicts that Salmonella are detected in 0.4% of the samples from feed mills, 0.4% in vegetable origin and 0.5% in domestic rapeseed. The mostly common finding in feed mills is S.typhimurium so this is a risk factor for environment and livestock. It shows the control of Salmonella in feed was sufficient (16).

### 4.1.1.2 Salmonella Control in Food-producing

The Swedish Poultry Meat Association represents 99 % of all broiler meat producers in Sweden. Salmonella control is made on red and white meat and started in 1961. It has continued in spite of the growing industrialization of animal production. The main goal is deliver Salmonella free products to consumers. There is a law that makes it mandatory for all veterinary laboratories to report immediately any isolation of Salmonella to the Swedish Board of Agriculture (SBA) and to the County Administration. Regardless of serovar, all of the isolates must be sent to the SVA for confirmation and registration. SBA will send a veterinary officer for investigation of the outbreak and supervising the clearance of the farm from Salmonella contamination. It is important that the restrictions on the infected farm remain in place until all animals are declared free from Salmonella. Destruction of the infected animals has been the only alternative to clear Salmonella from an infected flock (17).

### 4.1.1.3 Salmonella Control in Poultry

Salmonella control in broilers for slaughter is done 1-2 weeks before slaughter by choosing two pair of sock samples per flock (Table 1). In the hygienic program for poultry farms, all broilers are analyzed for Salmonella before slaughtering. Prevalence of Salmonella contamination above 5% is indicator for destroying the flock. Cost for destruction of Salmonella contaminated flocks is paid by the producers through insurance. Highest level of rules for hygiene and management procedures applies to breeder-flocks and hatcheries. A veterinary officer is in charge of the control for each farm and obligated to visit the farm at least yearly and take the official samples and make
sure of complying with the rules of the control program (Table 1). The principle "all in - all out" controls are carried out thoroughly after the clean-up of a poultry house contaminated with Salmonella. In Sweden there are strict rules concerning the location, construction of the building, the management of the birds, imported birds, and staying in quarantine under authorization by SBA. There are obligation regarding breeder flock and the eggs for hatching. Current strategy for the control is to detect as early as possible in the production chain (17).

Nowadays there are two methods of Salmonella control named as mandatory and voluntary. The mandatory control includes testing pre-slaughter and at the hatcheries in accordance with the zoonosis directive in force. The voluntary Salmonella control includes the animal environment, the houses, and hygiene programs. The farms and factories are responsible for any costs that result from Salmonella positive samples. This can lead the factories and farmers towards more comprehensive control and monitoring of their productive systems (17).

Severe outbreaks of human Salmonellosis originating from chickens necessitated the initiation of a Salmonella control program in poultry in 1970. Until 1984 about 90 % of the costs for the control were covered by the State and since 1984/85 the producer pays the control with the aid of an insurance program. The main principle of the control program is not to tolerate any Salmonella contaminated poultry or meat in the country. Prevention of entrance of contaminated animals is the first objective. The strategy consists of preventing Salmonella introduction through breeders, feed or the environment. Bacteriological monitoring is used for assuring the quality (17).

Table 2 shows sampling frequency and samples type taken from poultry farm in the surveillance program (16).
Table 2: Sampling scheme for Salmonella in poultry

<table>
<thead>
<tr>
<th>Category of poultry</th>
<th>Sampling frequency</th>
<th>Sample type</th>
<th>Sampling before slaughter</th>
<th>Official veterinarian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breeders in rearing</td>
<td>1 d. 4 weeks, 2 weeks prior to rearing or moving</td>
<td>2 pairs sock samples</td>
<td>14 d before slaughter</td>
<td>Once a year</td>
</tr>
<tr>
<td>Breeders in production</td>
<td>every 2nd week</td>
<td>5 pairs sock samples</td>
<td>14 d before slaughter</td>
<td>3 times under production</td>
</tr>
<tr>
<td>Layers in rearing</td>
<td>2 weeks prior to moving</td>
<td>2 pairs sock samples or 2 faecal samples of 75 g</td>
<td>14 d before slaughter</td>
<td>Once a year</td>
</tr>
<tr>
<td>Layers in production</td>
<td>every 15th week (start at 22-26 weeks)</td>
<td>2 pairs sock samples or 2 faecal samples of 75 g</td>
<td>14 d before slaughter</td>
<td>Once a year</td>
</tr>
<tr>
<td>Poultry for meat production (all species)</td>
<td></td>
<td>2 pairs sock samples or 2 faecal samples of 75 g</td>
<td>14 d before slaughter</td>
<td>Once a year</td>
</tr>
</tbody>
</table>

Source: SVARM 2009

4.1.1.4 Salmonella Control in Slaughterhouse

In red meat cutting program around 3000 samples of crushed meat and meat scrapings are taken and analyzed each year and around 1200 out of them are from white meat cutting (16).

Around 28000 samples from cattle, poultry, adult swine and fattening pigs are taken annually. The samples are taken from the cattle and swine carcass especially from intestinal nodes and swabs for poultry carcass and from neck skin (16).

4.1.1.5 Salmonella Control in Animals

For animals, vaccinations are not used. Only Salmonella free animals are sent to slaughterhouses. From breeding pigs, faecal samples are taken annually and twice a year from sow pools. Calves under six months undergo necropsy. Imported and individual animals are tested for Salmonella while wild animals were necropsy at SVA. All positive sample case is sent to SVA for authorization, resistance test, serotyping (16).
Table 3 shows number of infected poultry, the species, production stage and serotype of Salmonella in 2009 (16).

**Table 3:** poultry flocks infected with Salmonella in 2009

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Phagotype</th>
<th>Species</th>
<th>Production stage</th>
<th>Production type</th>
<th>No. infected flocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Agona</td>
<td>not relevant</td>
<td>Gallus gaius</td>
<td>Production</td>
<td>Meat production</td>
<td>1</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>RDNC</td>
<td>Gallus gaius</td>
<td>Production</td>
<td>Meat production</td>
<td>1</td>
</tr>
<tr>
<td>S. Goldcoast</td>
<td>not relevant</td>
<td>Gallus gaius</td>
<td>Production</td>
<td>Meat production</td>
<td>2</td>
</tr>
<tr>
<td>S. Sandiego</td>
<td>not relevant</td>
<td>Turkeys</td>
<td>Production</td>
<td>Meat production</td>
<td>3</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>RDNC</td>
<td>Turkeys</td>
<td>Production</td>
<td>Meat production</td>
<td>1</td>
</tr>
<tr>
<td>S. Livingstone</td>
<td>RDNC</td>
<td>Gallus gaius</td>
<td>Production</td>
<td>Egg production</td>
<td>1</td>
</tr>
<tr>
<td>S. diarizonae</td>
<td>not relevant</td>
<td>Gallus gaius</td>
<td>Production</td>
<td>Egg production</td>
<td>1</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>RDNC</td>
<td>Ducks</td>
<td>Production</td>
<td>Meat production</td>
<td>1</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>RDNC</td>
<td>Geese</td>
<td>Production</td>
<td>Meat production</td>
<td>5</td>
</tr>
<tr>
<td>S. Typhimurium</td>
<td>RDNC</td>
<td>Geese</td>
<td>Breeding</td>
<td>Meat production</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: SVARM 2009

4.1.1.6 *Salmonella Control in Humans*

Sweden started to collect the statistical data for Salmonella in humans from 1875. Every year around 3000–4000 cases of human salmonellosis are reported but 80–85% cases are related to the travel of people abroad (16).

Results from data on humans in 2009 show that, travel infections significantly decreased by 31% and domestic by 13% as compared to 2008. Figure 4 shows that domestic case of Salmonella is low and it reflects a low level of Salmonella in animals and food and constructive for many years (16).
Figure 4: Notified human cases of salmonellosis in Sweden 1988-2009.

Source: SVARM 2009

4.1.1.7 Antibiotic resistance control

The feedstuffs act limited the use of antibiotics for veterinary purpose from 1986. Total yearly sales of antibiotics in animals decreased from 1999 to 2008 from 18,237 kg active substance to 16,365 (Figure 5).
The Swedish parliament decided to implement a strategic program for control of antimicrobial resistance in 2007. This program involved human and veterinary medicine and its aim is to preserve the efficacy of antibiotic treatment (Figure 6).

The Swedish Strategic Program against Antibiotic Resistance (Strama) is a successful example of coordination (www.strama.se). Strama of Veterinary and food or Strama VL has been active since 2008. The main tasks of Strama VL are to coordinate the use of antibiotic in veterinary and food sections and set prioritization (18).
Boqvist et al., (2003) presented a paper on Salmonella data from animals, feedstuffs and feed mills in Sweden between 1993 and 1997. The number of 555 isolates was recorded from animals, representing 87 serovars. Of those 30 serovars were found in animals in Sweden for the first time. S. typhimurium and S. Dublin were the most common isolates. These Salmonella isolates were resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline (19).

In swine the total number of isolated increased during these years and 8 different serotypes were found. The most common were S. typhimurium followed by S.Derby and S. infantis (19).

In fowl S.typhimurium was the most common serovar and in broiler S.Livingstone. In pet animals 13 serovars were found and S.typhimurium was the most common. In zoo, wild and farmed animals 13 isolates were found. 30% of all these isolates were related to snakes and lizards and the most common isolate was S.subspecies III and in turtles it was S.subspecies II. In feed products S.livingstone was most common and in raw vegetables S.Senftenberg, S.Mbandaka, S.agona, S.cubana and S.subspeciesI were recorded. They were mostly found in soybeans, meal and, maize and rapeseed products. In raw material from animals S.Senftenberg was most common. In the study they concluded that feed were an important source for Salmonella and with HACCP principals it would be possible to control Salmonella in feed (19).
Palmgren in 2002 studied the spread of Salmonella in wild birds in Sweden. Black-headed gull is a main transporter of Salmonella amongst wild birds and S.typhimurium is the main serotype. Migrating birds might be vectors for both Salmonella and antibiotic resistance from other European countries (20).

Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) 2008 provided documents which prove the favorable situation of antimicrobial resistance in Sweden. The total amount of antibiotics used for animals were 16 365 kg in 2008 which is similar to year 2005 and among the lower figures this decade. Antibiotics are the most important reason for resistance. The amount of antibiotics for in-feed or in-water medication has decreased by 93% since 1984 and is today but 15% of the total sales. The sales of Fluoroquinolones has decreased by 16% over the last three years which is explained by decreased use both of injectable products (mainly for food producing animals) and of products for oral medication of individual animals. Salmonella is rare in Swedish animals and most incidents involve susceptible strains. There are no indications of increased occurrence of resistance. In 2008, 85% of the strains were susceptible to all antibiotics tested and only six of 85 strains from food producing animals and one of 20 strains from pet animals were multi-Resistant. Resistance to Third generation cephalosporin was not observed but Fluoroquinolone resistance was confirmed in one isolate from a pig sampled at slaughter. That strain was not re-isolated from pigs from the herd of origin (18).

The 2009 report from SVARM showed that the situation of AMR in bacteria of animal origin remained favorable from an international perspective. The total amount of antimicrobials used for animals was 15 368 kg in 2009 which is the lowest figure in 30 years. It was reported that the prevalence of Salmonella was rare in Swedish animals and most incidents involved susceptible strains. 91% of the strains were susceptible to all antimicrobials tested and just 4 of 74 strains from food producing animals and 2 of 24 strains from pet animals were multi-resistant. Resistance to Third generation cephalosporin was not observed. Alertness towards resistant Salmonella in food-producing animals was reasonable. The three incidents of multi-resistant Salmonella subspecies I were seen in cattle (16).
The 2010 report from SVARM shows that antibiotic resistance in bacteria from animals remains rare with suitable control programs. However it is essential to monitor regularly any new changes of resistance and report the trends. According to the SVARM 2010 report, the total amount of antibiotics used for animals was 14 177 kg in 2010 which is the lowest form in 30 years. The remarkable improvement in “prudent use” of antibiotics for pet animals is a good example of showing the results of a continuous monitoring in catching the current problems and finds a solution in a reasonable time. Based on SVARM 2010, Salmonella is not frequent in Swedish animals and the majority of Salmonella are susceptible strains. In 2010, 87% of the strains were susceptible to all antibiotics tested and only 6 of 62 strains from food producing animals were multi-resistant. There are no denotations of increased occurrence of resistance but there is a risk of resistant Salmonella in food-producing animals in the future. This is emphasized by the incidence in later years of multi-resistant monophasic Salmonella subspecies I, O 4, 5, 12: i- in animals (36).

Olsson-Liljequist et al. evaluated the Antibiotic Consumption and Resistance in Sweden in 2008. The Swedish Institute for Infectious Disease Control (SMI) and the Strama has presented annual reports on antibiotic use and resistance in human medicine since 2001. Data on antibiotic consumption are collected from the National Pharmacy´s Database and the Swedish Register of Prescribed Drugs was used for data regarding antibiotic consumption. The consumption of Quinolones and Cephalosporin decreased dramatically. The new guidelines could be effective towards bringing about changes such as for the treatment of lower urinary tract infections in women, for the treatment of community-acquired pneumonia and for reducing the selective pressure on ESBL-producing bacteria in the hospitals. Sweden successfully combated the major outbreaks of resistant bacteria. However, ongoing outbreaks of Vancomycin-resistant Enterococcus Faecalis (VREF) and Enterococcus Faecium in hospitals and a general increase in ESBL-producing Enterobacteriaceae still are source of concern (21).
4.1.2 Denmark

Denmark had the program for control of Salmonella resistance in healthy animals, slaughters, food and human. They started ban of growth promoters in animals’ food and to control consumption of antibiotics from 1995. They studied relationship between consumption of antibiotics and incidence of resistance events (22).

This Result part shows strengths and weaknesses of monitoring and control programs in Denmark and described the situation regarding Salmonella enterica and antibiotic resistance in Europe.

Bager reviewed the function of the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) in the year 2000. Monitoring the source of infection, the use of antimicrobial drugs and the relationship between the use of antibiotic drugs and resistance events are assessed. DANMAP is a registration system for the results of testing the strains from all animal or human sources. The susceptibility to representatives of the major classes of antibiotics is examined in 3 isolate samples and all of the isolates are stored. All of the data are based on minimum inhibitory concentration (MIC) values or millimeter inhibition zones. The whole system is a comprehensive and efficient in tracking all the changes in the trend of antimicrobial resistance (22). The effect of antibiotic consumption on resistance will be tracked by recording all the details for further use. In animals, samples collected from slaughter and population, monthly of pigs and cattle and weekly of broiler. One sample was taken per herd or flock. Furthermore Salmonella was found in food of pigs so it was a risk factor. Monitoring of antibiotic consumption was an important part in DANMAP. Only resistance monitoring was not enough for well-objected intervention. The program needs information about consumption of antibiotics and resistance data too. Phenotypic expression of resistance may be happen of co-selection with unrelated compounds because of some resistance genes linked to cross-resistance to related antibiotics. About 80% of medicines in veterinary practice are sold on prescriptions and there is no information on consumption in the individual animals. Therefore attention must be paid on the non-antibiotic mediated transmission of resistance subtypes within a bacterial genus and cross-resistance; it often results in resistance to other antibiotic (22).
Hammerum et al., (2007) reviewed DANMAP. The importance of antibiotic resistance agents as an emerging problem around the world has led to the initiation of antibiotic agent resistance monitoring programs in several countries. In 1995, Denmark established a comprehensive monitoring system for antibiotic drug usage and antibiotic agent resistance in animals, food, humans; studying association between antibiotic consumption and antibiotic resistance and identifying ways of transmission and new fields of research for future. DANMAP was organized at the plan of the Danish Ministry of Health and the Danish Ministry of Food Agriculture and Fisheries as an organized national monitoring and research program (23).

The application of antimicrobial growth factors (like Avoparcin) in 1994 was more than half of the total antimicrobial drugs in Denmark (figure 7). Growth promoters were used as an in-feed supplement for all broilers like chicken and pig farms. Ban on Avoparcin had a substantial effect on lowering the occurrence of Vancomycin-resistant Enterococcus Faecalis (VREF) isolated from fecal samples from broilers chickens. No significant change in the occurrence of VREF in pigs was observed in the first years after the ban of Avoparcin. Decrease in the consumption of macrolides (Tylosin) as growth promotion in 1998 caused significant decrease in the occurrence of VREF among Enterococcus faecium isolates from pigs in 1999 and 2000, which shows the continuous use of macrolides, mainly Tylosin was responsible for producing antibiotic resistant (23). The figure 7 shows the effects ban of antibiotic growth promoters in prescribed veterinary and human antibiotic agents.
Figure 7: Consumption of prescribed antimicrobial agent and growth promoters in animal production and prescribed antibacterial agent in human, Denmark, 1990-2005.
Source: DANMAP 2007

Another program was limited to use fluoroquinolones for animals from 2002. DANMAP didn’t check pet animals in contrast to Sweden and Norway. For pets fluoroquinolone and cephalosporin is used so the transfer of resistance bacteria or resistance determinate is possible (23).

The imported poultry and pig meat had a higher prevalence of resistance Salmonella. In additional travel to another country transferred antibiotics resistance agents to Denmark (23).

National intervention program 1997-2005 in Denmark decreased the rate of Salmonella but imported meats were not including in this program; these products were just monitored randomly. Ready products and food products were not necessarily free Salmonella. The complexity of relationship between antibiotic agent and resistance in the food supply and human foodborne infections is a source of concern in Salmonella control. The level of resistance of bacteria in domestic food, imported food and the influence of travel abroad are most important factors for transfer. The surveillance systems of antibiotic consumption and resistance in animals and humans are necessary on a universal level because food, humans and even livestock are transported.
Evidenced-based research is needed to facilitate further regulation regarding antibiotic agent resistance and antibiotics consumption. Monitoring of antibiotic drug resistance and a range of research activities related to DANMAP have contributed to restrictions or bans the use of several antibiotic agents in animals’ food in Denmark and other European countries. It shows that international collaboration is important for control diseases (24).

Bruun et al., (2008) published a report on an independent outbreak of Salmonella Typhimurium infection characterized in the Multiple-Locus Variable amount of tandem repeats analysis (MLVA) method by a separate report in Denmark, Norway and Sweden. In Denmark 37 cases were recognized and multiple outcome strain in pork, pigs and different products as the resource was identified. In Norway, 10 cases were recognized and meat was the probable source. In Sweden 4 human cases were recognized and 2 isolates from minced meat with the separate profile were found. Meat showed that it most probable originated from Denmark. European Center of Disease Control (ECDC) was successful in connecting the outbreaks in the different countries and follows the source. This outbreak demonstrate that good worldwide communication channels, early alerting mechanisms, cooperation between public health and food safety agency and synchronized molecular typing tools are important for effective identification and management of cross-border outbreaks. Differences in legal requirements for food safety of neighboring countries may be a challenge in terms of communication with consumers in areas where cross-border shopping is common (27).

Salmonellosis was the second most common zoonotic disease in the European Union (EU) reported by The European Food Safety Authority and European Center of Disease Control (EFSA/ECDC) during 2007. In 2004-2005 prevalence of Salmonella in laying hens detected 30.8% in EU. The incidence of Salmonella varied from 0% in Sweden, Norway and Luxemburg, 0.4% in Finland and 2.7% in Denmark to 79.5% in Portugal. In 2005-2006 prevalence of Salmonella in broiler flocks was 23.7% in EU. The incidence of Salmonella varied from 0% in Sweden, Finland and Norway, 1.6% in Denmark and Slovenia to 68.2% in Hungary. In 2006-2007 prevalence of Salmonella in turkeys for slaughter was 30.7% and in turkeys for breeding was 13.6% in EU. The incidence of Salmonella in turkeys for slaughter varied from 0% in Sweden, Finland, Norway, Bulgaria, 4% in Denmark to 78.5% in Hungary. In 2006-2007 prevalence of Salmonella
in lymph node samples from pigs for fattening was 10.3% and for swab samples was 8.3% in EU. The prevalence of lymph node samples ranged from 0% in Finland, 0.3% in Norway, 1.3% in Sweden and 29% in Spain. The prevalence for swab samples was 0% in Sweden, Slovenia and 20% in Ireland. In 2008 prevalence of Salmonella in fattening herds was 33.3% (0-55.7%) and in breeding herds was 28.7% (0-64.7%) in EU. It was varied 0.5% in Sweden and Norway, 0% in Finland and 40% in Denmark. In 2008 prevalence of Salmonella in broiler carcasses was 15.7% in EU. The survey showed Sweden, Finland and Norway had favorable Salmonella compared to other EU countries (48).

Hello et al., (2011) published a paper about worldwide spread of an epidemic population of Salmonella enterica serovar Kentucky ST198 resistant to Ciprofloxacin. National Salmonella surveillance systems during 1999-2008 demonstrated high-level resistance to Ciprofloxacin in Salmonella enterica serovar Kentucky from France, England and Wales, Denmark and the United States. The total of 497 S. enterica Kentucky characterized from France, 698 from England and Wales, 114 to Denmark, and 697 to United State. Isolates belonged to a single clone. The resistance can spread easily to other serovars so monitoring program and exchange of information between the countries is necessary. During the same period, 1.6 million cases of Salmonella were reported in 27 European countries. In North America estimated 1.7 million cases and 2800 fatalities per year. This clone was probably selected in 3 steps in Egypt during the 1990s and the early 2000s and now spread to several countries in Africa, and more recently in the Middle East. Poultry are susceptible for infection by this clone. It is concluded that continuous surveillance and desirable control measures is necessary to limit the spread of this strain (30).
4.2 USA

4.2.1 Control programs in USA

The National Antibiotic Resistance Monitoring System (NARMS) organized in 1996 by the Food and Drug Administration (FDA), The Center of Disease Control and prevention (CDC), Food Safety Inspection Service (FSIS) and the United State Department Agriculture (USDA). The goal was to monitor the antibiotic susceptibilities of zoonotic enteric pathogens in infected human and animal, healthy animals and body of food-producing animals in slaughter (31). They wanted to present explanatory data on the area and time trends of antibiotic susceptibility. The Foodborne Active Surveillance Network (Food Net) performs surveillance and for completing this program, the national Food Safety Initiative (FSI) started for reduces foodborne diseases. The FSI must adopt the surveillance, Investigation, risk estimation, research, education, outbreak management and strategic planning. In 1998 USDA increased sample collection in slaughter plants by performance HACCP program (31).

FDA suggests the Idea for evaluating National Antibiotic Resistance Monitoring System (NARMS) follow as:

- Taking human sample has bias because handling samples, clinical laboratories and physicians’ choice are different so stratification sample be good.
- Initially assess antibiotic resistance of intestinal flora of healthy individual then chose sampling of healthy population is easy.
- Large sample size and national sampling policy of retail meat help to respond specific, hypothesis query and studies.
- HACCP program make really nationally reprehensive plans (10).
4.2.2 Salmonella Resistance in USA

Angulo et al., 2004 from USA showed the indication of a connection between use of antibiotic agents in animals’ food and antibiotic resistance amongst bacteria isolated from humans and the cause of resistance. They confirmed that the use of antibiotic agents in animals’ food could be linked with antibiotic resistance amongst bacteria isolated from humans. The antibiotic resistance was indicated among Salmonella and Campylobacter isolated from humans. Human health cause include: uncommon infections that would not have occurred and increased rate of treatment failure and increased severity of infection. Lengthy period of illness, increased rate of septicemia infections, lengthy hospitalization and higher mortality were observed (32). Samples of S.Typhimurium DT104 in cattle were analyzed for antibiotic resistance to tetracycline, chloramphenicol, fluoroquinolones, and nalidixic acid. Antibiotic resistant infections were seen in people that visited or lived at farm. Resistance to Nourseothricin found in human Salmonella isolated (32).

In a recent study it was estimated that one million cases of Salmonella disease that occur each year in the United States. It was projected that resistance in Salmonella may cause about 30 000 additional cases, lead to about 300 additional hospitalizations and ten additional deaths (32).

In 2003 about 10,108 tons animal’s antibiotic was sold in USA with Ionophore/Arsencal 42.8%, Tetracycline 32.6%, Cephalosporin and Macrolid 18.95%, Sulfonamide and Penicilin 3.7%, Amino glycoside and Fluoroquinolone 0.2% (24). Multi-resistance of Salmonella increased from 6.3% to 21.4% in USA from 1999 until 2005 (9).

Isolates of Salmonella in dairy cattle showed resistance to Ampicilin, Ceftiofur, Chloramphenicol, Streptomycin and Tetracycline that was 62.9%, 49.5%, 56.4%, 63.2% and 65.5% respectively in 2003 (9).

Isolates from chickens with Salmonella had increased resistance to Amoxicillin, Clavulanicacid, Ceftifur, Cefoxitin and Tetracycline and, decreased to Gentamicin and sulfa (24). Isolates from other birds were resistant to more than 5 antibiotic but 79% of isolates from organic material were sensitive to 17 antibiotics (9).
Lynn et al., 2008 characterized the genetic basis of Multi-Antibiotic Resistance (MAR) in Salmonella serovar Newport isolates collected from food animals in the United States during 1997-2003. They found an increase of Salmonella from 4.6%-10.3% and multidrug resistance. The number of 19 genes related to 12 antibiotic resistances were isolated was from cattle and pigs. Resistance was seen to Ampicilin, Cephalothin, Cefoxitin, Ceftifour, Amoxicillin-clavulanic acid, Cetrixone, Streptomycin, Sulfisoxazole, Trimethoprim, Sulfamethoxazole, Chloramphenicol and Tetracycline (33).

Greene et al., 2008 analyzed the distribution of MDR S.typhimurim and S.Newport in USA was done in 2003-2005. Of 1195 S.typhimurium isolates, 60% were susceptible, 28 (24%) were MDR-ACSSut (ampicilin, cholramphenicol, streptomycin, sulfonamides, tetracycline) and of 612 S.Newport isolates, 80% were susceptible and 97 (16%) had MDR-AmpC (additional amoxicillin, clavulanicacid, ceftiofur and ceftriaxone).There was no significant difference in sex, age and regional distribution of patients with susceptible or MDR-ACSSut strains of S.typhimurim. There was a significant difference in seasonal distribution overall and within regions between susceptible and MDR-ACSSuT strains. There were significant differences in regions and age between MDR-AmpC and susceptible S.Newport isolates. Regions that have more cattle and milk cow density had more MDR in both serotypes. The southern states of USA had the lowest percentage of S.Newport isolates with MDR and also the smallest population of milk cows. Susceptible S.Newport isolates were more common than MDR isolates in patients <2 years. In both serotypes MDR isolates showed less seasonal difference than susceptible isolates. Susceptible isolates and MDR of S.Newport had a significant difference in the age distribution of the patients (34).

Joseph et al., 2009 studied the prevalence and categorization of Salmonellae in commercial ground beef in the United States. 4,136 samples with prevalence of Salmonella in ground beef to 2.4% according to surveillance done 2005-2007 in USA. An outbreak of MDR S.Newport strain related to ground beef was reported in 2002. In this study overall prevalence of Salmonella was 4.2% and serotypes Anatum, Mbandka, Montevideo and Muenster represented half of the isolates. The most common serotypes reported in humans in United States are Typhimurium, Enteritidis, Heidelberg, Newport and Javiana. In the study they found Salmonella with antibiotic resistance to tetracycline
and sulfisoxazole. Serotypes Agona, Dublin, Newport, Reading and Typhimurium were MDR but all serotypes were susceptible to aikacin, ciprofloxacin and trimethoprim-sulfamethoxazole and, MDR Salmonella was 0.6 % (15).

Sjölund-Karlsson et al., 2011 studied 696 isolates of non-typhi Salmonella collected from humans, animals’ food and retail meats in the United States for antibiotic susceptibility to azithromycin. Emerging resistance to traditional antibiotic agents lead to use of azithromycin for the treatment of invasive Salmonella infections. The isolates were from humans, animals’ food and retail meat. 232 non-typhi Salmonella isolates and 72 S. typhi isolates were selected. Among non-typhi isolates, S. enteritidis in humans, S. Kentucky in animals’ food and S. Heidelberg in retail meat was most common. In chicken, cattle, ground turkey, chicken breasts and in retail meat a higher prevalence of Salmonella isolates were found. 9.2% of the isolates were resistant to ceftriaxone and all were sensitive to azitromycin (35).

5. Discussion

This study shows the prevalence of Salmonella enterica and antibiotic resistance of that is high in Europe countries and USA except Sweden. All countries have different control programs for that but the results in veterinary shows that Salmonella are rare and favorable only in Sweden where 87% of the strains were susceptible to all antimicrobials tested. Also domestic case of Salmonella in human are low and it reflects a low prevalence of Salmonella in animals. In most of the cases of Salmonella, travelling to other countries might result in the outbreak of this disease by food and etc. (16).

The control of Salmonella and antibiotic resistance are closely related to each other. It means, the control of Salmonella in animal, animals’ food, environment and humans is the best possible way for control of antibiotic resistance. The most important cause of antibiotic resistance is consumption of antibiotic as a growth promoter and treatment for animals and human. Therefore it is very important decrease the consumption of antibiotic in animal and humans.
The effective strategies for *Salmonella* control in Sweden are:

- Prevention from Salmonella contamination in all parts of the production chain.
- Monitoring the production chain at critical points for detection any source of Salmonella contamination.
- Undertaking actions necessary in detecting Salmonella cross contamination.

The creation of a legal framework and motivations to ensure co-operations and compliance with the program is the first priority (17).

Sweden is successful in controlling Salmonella and antibiotic resistance by the implantation of the following programs.

They started control programs early in year 1950. Under these programs all animal food and factories are covered by GMP and HACCP system. Cooperation between different organizations as SVA, RASFF, Poultry Meat Association, SBA, County Administration, veterinary officer; and immediate reporting is responsible for the success of these programs. The program involved the owner of farms and factories and it could lead towards more comprehensive control and monitoring of their productive systems. They had consecutive and specific programs for taking samples of feed, meat, animals, food (17).

Using effective strategies against antimicrobial resistance is a lesson from the experience of countries like Sweden and other countries. Monitoring, regular data registration and collection, appropriate educations are necessary elements for combating AMR. Antibiotic resistance is a universal public health problem which affects the health status of human and animals. Global team working and experience sharing should be implemented. We need a strong foundation of collaboration and coordination. Strama VL tries to increase the level of knowledge through the main problem and provide reasonable (18).

The control program of antibiotic resistance is multifaceted and involves: monitoring antibiotic and antibiotic resistance, prevention of infection, prudent use of antibiotic and non medical. Increase knowledge, international work between countries and involve human and animals are the success key factors. Further the limited use of antibiotic for
animals and humans specially Quinolone and Cephalosporin was also another factor for the success.

Low consumption of antibiotics in animals and humans; the low prevalence of Salmonella due to strict control programs result in a relatively low frequency of antibiotic resistance in isolated strains of Salmonella in Sweden.

Denmark on the other hand is the first country in Europe that set up a systematic monitoring program of antibiotic consumption and antibiotic resistance in animal, food and humans. However this program was not successful like as Swedish program. They started ban of using growth promoter in animal food from 1995, and most of the European countries started the ban later. The following are the reasons:

- An obvious reason for some parts of the failure in Danish control of Salmonella compared to Sweden is related to the delay in establishing the monitoring system (44).

- Monitoring bacteria originated from pet animals are obtained in Sweden and Norway but not in Denmark (42). Use of fluoroquinolone and cephalosporin in treatment of pet animals in Denmark is important (43). A transfer resistant bacterium to fluoroquinolone and cephalosporin from pet animals to humans seems possible and should be considered as a source of contamination and is a reason for modification of the Danish surveillance system (23).

- They didn’t sell all medicines in veterinary on prescriptions. Just around 80% of medicines were available on prescriptions and they didn’t have any information on the consumption in the individuals and animals (22).

- They didn’t control imported meat for salmonella but just monitored randomly. It wasn’t necessary that ready products and food products to be free of Salmonella. Denmark imported meat from different country so it was possible transfer of different sources of Salmonella (23).

- The ban of growth promoter in animals’ food was not success in Denmark and European countries. The study showed increase of antibiotic resistance among animals and humans after ban. The ban of growth promoter followed by increase
of morbidity, bacterial infection, mortality and foodborne bacteria illness in animals and humans so the antibiotic consumption increased in animals and humans then increase antibiotic resistance (28).

Cox and Ricci 2008 raised a question regarding causal regulations vs. political will. They showed after ban of antibiotic as growth promoter in animal feed, increase of antibiotic resistance among human and animals. Then they used Quantitative risk assessment (QRA) modeling for finding the reasons of illness and antibiotic resistance. This model is a great framework for perceptive and clearing up interventions and outcome causally, and identifying ways to control prospect hazards in effect. Latest experience from some European countries shows insignificant advantage of ban growth promotion. The DANMAP annual reports found the antibiotic resistance rates in human increased significantly after ban of growth promotion. When diseases and antibiotic resistance increased in Europe, it fell significantly in USA. Effective factors in USA were achievement of HACCP in food chain, increase public knowledge, education and prudent antibiotic and promoter by farmers. The QRA model showed the use of antibiotic increase health and resistance agents in animals. Without antibiotics, illnesses in animals and microbial loads of zoonotic pathogens in meat will increase. Then consumption of antibiotic will increase in human and, increase of antibiotic resistance and, expulsion of resistance agents to sewage, water and soil. Then antibiotics and resistance agents will spread to environment, other human and animals. The QRA model predicts that ban of antibiotic in animal, increase resistance agents in humans (28).

DANMAP has led the changes in use of antibiotic in Denmark and other countries. Applying a fully comprehensive monitoring and evaluation or surveillance among European countries could detect every small change in microbial resistance in Salmonella. Until now the effects in Denmark had been seen mostly in animals but needs more awareness for humans as well. One of the strengths of DANMAP is cooperation between veterinary and human healthcare providers, thus offering a broad range of viewpoints and professionals. This integrated program was made possible because access to all relevant data and samples that were already systematically collected from animals, food and humans has been shared. The dependency of Denmark in importing food items urges appropriate approach for difference and future changeless (23).
In 2000 DANMAP reported the use of antibiotic agents increased by humans both outside and inside hospitals (38). Until that time, antibiotic consumption was the lowest in Europe like as Germany, Sweden and Austria (40). Since then the mean antibiotic consumption in hospitals has increased by 39% (41). Another reason for the increase of consumption has been related to using higher doses of antibiotics based on better knowledge of the pharmacokinetic and pharmacodynamic properties of the drugs (23). In addition, high level consumption of antibiotic agents and newer antibiotic agents with broad spectrum are the other sources of concern, e.g., Cephalosporin, Fluoroquinolones, and Carbapenems (41).

The complexity of the relationship between antibiotics consumption and antibiotic resistance in the food supply and in human foodborne infections is a source of concern in Salmonella control. The level of antibiotic resistance of bacteria in domestic food, imported food and, travel to abroad are the most important factors. The surveillance systems of antibiotic consumption and antibiotic resistance in animals and human must be necessary and universal because of, transfer of food, human and even livestock. Evidence-based research is needed to facilitate further regulations regarding antibiotic resistance and consumption. Monitoring antimicrobial drug resistance and a range of research activities related to DANMAP have contributed to restrictions or bans of several antimicrobial agents in animals’ food in Denmark and other European Union countries. It shows that international collaboration is important for control of diseases (24).

Since 1998, Denmark showed more levels of resistance from imported foods than Danish food (37). Denmark has higher levels of antibiotic agent resistance and higher levels of imported meat products with different foreign origin. DANMAP 2000 reported higher levels of resistance with related to travel (38). From 2001 through 2005, the number of abroad travels increased for Danish travelers and the most popular destinations were Spain, France, Italy, the southern part of Europe and Asia which are high-risk areas for acquiring antibiotic-resistant foodborne zoonotic infections (39).

Another study showed Salmonella and antibiotic resistance was a big problem in Europe because of lack success control programs. EFSA-ECDC annual report of zoonotic infections in 2007 declared Salmonella was the second infection with 151,995 human cases. Salmonella Enteritidis was most common serovar (29).
A study in Britain from 2004-2007 showed the high level of Salmonella and antibiotic resistance in different animals (45). In 1969, the Swane Committee recommended to the British government that, antibiotics for human should not use for animal (46). The epidemic of Salmonella enteric, serovar Kentucky ST198 resistant to Ciprofloxacin in some countries of Europe and USA is the reason of undesirable control programs (30).

USA in control of Salmonella enterica and antibiotic resistance wasn't successful. In USA control program of Salmonella and antibiotic resistance was done with collaboration between different organizations. USA had more focus to decrease the prevalence of Salmonella, increase knowledge achievement of HACCP in food chain and, prudent consumption of antibiotics and growth promoters (31). They did not limit the consumption of antibiotic in animals so; it could create multiple resistances (9).

Evidence-based documents of USA in 2004 show association between consumption of anti-microbial agents in animals' food with anti-microbial resistance among bacteria isolated from humans. It shows transfer of antibiotic resistance from animals to human by consumption of meat and contact with animal (32).

Application of Bambermycin (flavophospholipol) because of capability of inhibits transglycosylase and cell wall synthesis, might be another useful approach in combating antibiotic resistance. Bambermycin is used as a feed additive growth promoter in cattle, pigs, chickens and turkeys but has no therapeutic use in humans and animals. It has also been shown in decrease transferable resistance in pathogens and the shedding of pathogenic bacteria such as Salmonella in pig, calves and chickens (47).

Wray and Gnanou 1998 evaluated the monitoring methods of antibiotic resistance of bacteria from animals in 12 European countries. Generally disk diffusion method was effective and the possibility of strong coordination in the surveillance systems was approved among European countries (25).

Caprioli et al., 2002 studied on monitoring of antibiotic resistance in bacteria of animal origin in Italy. The aim of study was to define the minimum of epidemiological and microbiological requirements for establishing a surveillance program for antibiotic resistance of bacteria with animal origin. They found different bacterial species include,
veterinary pathogens, zoonotic pathogens and commensal bacteria should be used as indicators in surveillance processing. Up to date data and final reports should be available for veterinarians and regulatory authorities. Follow-up of the results would be a useful tool for developing guidelines for the further use and choosing the desirable action strategies (26).

6. Conclusion

This study shows a strong relationship between antibiotic resistance of Salmonella enterica and control of these bacteria in animals. The most common reason of antibiotic resistance is consumption of antibiotics in animals. Antibiotics for human use should not be animal-like antibiotics. Therefore low amounts of antibiotics are used to control Salmonella in animals and humans. Low consumption of antibiotics in animals and humans; the low prevalence of Salmonella due to strict control programs result in a relatively low frequency of antibiotic resistance.

The control program must be consider for animal, animal’s food, food, environment and Human. It should be continuously and intensive on critical points. The degrees of communication between veterinary organizations and health care providers are important in order to exchange the knowledge and relevant information.

The control program of antibiotic resistance must be multifaceted and involves: monitoring antibiotic and antibiotic resistance, prevention of infection, prudent use of antibiotic and non medical. Increase knowledge, international work between countries and involve human and animals are the success key factors.

Different bacterial species include as veterinary pathogens, zoonotic pathogens and commensal bacteria should be used as indicators in surveillance processing. However, the importance of continuous monitoring as a detecting tool of new types of resistance agent is helpful. Also the use of reliable Quality assurance system is emphasized and the follow-up of the results would be a useful tool for developing guidelines and choosing the desirable action strategies. The correct choice of method for monitoring antibiotic resistance is important.
Good worldwide communication channels, early alerting mechanisms, inter-sectoral cooperation between public health and food safety agency and synchronized molecular typing tools are important for effective identification and management of cross-border outbreaks.

7. References

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