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Antimicrobial strategies in human and animal reproduction

Proceedings from a symposium in Uppsala, Sweden
May 7, 2009

Renée Båge, Matts Olovsson and Bodil Ström Holst *(editors)*

Uppsala, 2009

CRU Report 23

CRU CENTRE FOR REPRODUCTIVE BIOLOGY IN UPPSALA

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Foreword

On 7 May 2009 the symposium"Antimicrobial strategies in human and animal reproduction" is arranged by CRU, Centre of Reproductive Biology in Uppsala. CRU is a multidisciplinary network of almost 100 scientists with different academic backgrounds at SLU, Swedish University of Agricultural Sciences, and UU, Uppsala University.

The threat of infectious diseases has substantially decreased since the discovery of antimicrobial agents during the 20th century. Previously fatal infections can now be treated. The recent emergence and spread of microbes resistant to commonly used antimicrobials now poses a serious threat to human and animal health. Resistance to antimicrobials is a natural phenomenon that can be amplified or accelerated by a variety of factors. When anti-microbial agents are used incorrectly, the likelihood for resistance: that bacteria and other microbes will adapt and replicate rather than be killed, is greatly enhanced. Strategies on antimicrobial use are needed to ensure that efficient antibiotics are available also in the future, in the field of reproduction as in other fields.

On behalf of CRU we wish you welcome to take part of the symposium that covers both general aspects on antimicrobial resistance and resistance epidemiology, and presentations on antimicrobial strategies for specific disease entities. We have gathered speakers from both human and veterinary medicine in an attempt to enlighten comparative aspects and strengthen our common mission – broaden the knowledge on antimicrobial resistance mechanisms and scrutinise treatment regimes and policies within our respective fields of reproduction. We are looking forward to high quality scientific presentations as well as fruitful discussions.

Uppsala in April 2009

Renée Båge, Matts Olovsson and Bodil Ström Holst (editors)

ANTIMICROBIAL STRATEGIES IN HUMAN AND ANIMAL REPRODUCTION

Symposium Thursday May 7th 2009, Oscar II Conference centre.

Moderator: Matts Olovsson

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15.45-16.00	Antimicrobial strategies – mating and AI in horses	**Anne-Marie Dalin**
16.00-16.30	**Final discussion**	

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Antimicrobial resistance and disarming of medicine, resistance situation today and threats in the future.

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The emergence of antibiotic resistance is considered to be one of the major health threats for the citizens of Europe by the European Centre for Disease and Prevention, ECDC. The WHO also states that resistance is jeopardizing many of the achievements of modern medicine (such as cancer treatment, intensive care and major surgery). Resistance rates are growing rapidly all over the world. To meet this broad intersectorial international collaboration is urgently needed, as is rapid development of new drugs. A conference on innovative incentives for development of new antibacterials will be held during the Swedish EU presidency in September 2009.

Antibiotic resistance in bacteria – epidemiology and zoonotic aspects

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The introduction of antibiotics into human and veterinary medicine has had a major impact on both human and animal health. Antibiotic resistance in bacteria colonising one host species can spread to other species. Containing antibiotic resistance is part of the public health responsibilities of veterinary medicine.

Emergence and spread of resistant bacteria

Genetic changes

A bacterium that is naturally susceptible to an antibiotic can acquire resistance in two distinct ways: through mutation(s) in the relevant gene or through uptake of a copy of a resistance gene present in other bacteria.

Resistance to many antibiotics can occur by mutations. Resistance will be confined to the mutant clone and emergence and spread will depend on the clone's ability to multiply and infect new hosts (vertical transmission). This mechanism is not important in certain bacteria (e.g. *Mycobacterium tuberculosis*) or for specific antibiotics (e.g. quinolones), but for most agents it is not the clinically most important mechanism.

More common, and more important, is uptake of resistance genes (horizontal gene transfer). This can occur in different ways. Commonly, resistance genes are carried on small extrachromosomal loops of DNA (plasmids). Copies of a plasmid may pass from one bacterial cell to another. Even shorter mobile elements, transposons, may be carried either on a plasmid or in the chromosome. Transposons are able to 'jump around' in the chromosome or between a plasmid and the chromosome in the host cell. The flow of resistance genes is extensive and occurs also between bacteria that are phylogenetically very different (e.g. between enterococci and *Escherichia coli*).

Selection – use of antibiotics and resistance

In an environment exposed to an antibiotic, susceptible bacteria will decrease in numbers while resistant bacteria will continue to multiply. Prevalence of resistance will increase. In evolutionary terms, exposure to antibiotics exerts a selective pressure on bacterial populations, giving bacteria with advantageous traits (i.e. resistance) a competitive advantage (survival of the fit).

Co-transfer and co-selection

Plasmids and transposons may carry several resistance genes, each to a different class of antibiotics. All the genes will be transferred in the same event and this is called co-transfer. Exposure to any of these antibiotics will select for the presence of the entire genetic element. As an example, in *E. coli* genes for tetracycline, sulphonamides and streptomycin resistance

are often carried on the same plasmid. Use of either tetracyclines or streptomycin will favour the plasmid carrying strains and thereby emergence and spread of both all three resistance traits (co-selection).

The pool of resistance genes

Upon each treatment, not only the pathogen but also the entire normal flora is exposed to antibiotics. Resistance may be acquired by and selected for in commensals, or even in environmental bacteria. These will act as a reservoir of resistance genes, sometimes referred to as the pool of resistance genes. Unless specifically looked for, this reservoir will go unnoticed until the resistance genes pass into clinically relevant bacteria. Over the last 70 years, a powerful selective pressure has been applied on the microbial communities of the world. A large pool of resistant bacteria has been created and is constantly evolving, favouring more extensive spread of resistance genes within and between different ecological niches.

Some peculiarities of resistance epidemiology

Antibiotic resistance is a property of bacteria and naturally, its epidemiology will be influenced by the same factors that favour bacterial spread. This means that factors such as hygiene contact rate (crowding, trade), size and structure of host population(s) will influence. The selective pressure in a population is the major risk factor. Transfer of resistance genes through plasmids can be viewed as an infection where the bacteria are hosts. A plasmid, or the chromosome, can be 'infected' by a transposon. The fact that resistance epidemiology has at least two levels, maybe three, complicates analysis and epidemiological tracing. Further, the potential for co-selection must be considered. In view of this complexity, it is not surprising that the relation between antibiotic use and resistance is not always clear cut.

Zoonotic spread of resistance

Zoonotic spread of resistance can occur through spread of resistant bacteria or resistance genes. In both cases, food and direct contact are the two most important routes for spread. However, especially for resistance genes spread can occur wherever bacteria from different host species or ecosystems meet. Therefore, the possible routes of transmission are numerous (Figure 1).

Spread of bacteria - food

Nontyphoid salmonellae and campylobacters are two of the most common causes of food-borne illnesses. The emergence and spread of a multiresistant strain of *Salmonella* has caused considerable concern. Today, international spread of multiresistant strains with resistance also to 3rd generation cephalosporins (extenced spectrum betalactamases [ESBL] or plasmid mediated AmpC-type resistance) cause considerable concern.

Spread of bacteria - contact

Recently, methicillin resistant *Staphylococcus aureus* (MRSA) of a particular clonal complex, CC398, have emerged and spread among pigs and other intensively produced animals in Europe. In regions with a high prevalence of CC398 in animals, people in direct contact with these live animals (especially farmers and veterinarians, and their families) are at risk of colonisation and subsequent infection. The 'large animal associated MRSA' is a zoonosis in the sense that animals are the main reservoir for maintenance of infection.

Occurrence of MRSA in pets and horses is a well documented occupational hazard. The strains of MRSA in found in companion animals are generally the same as those commonly occurring in hospitals in the same geographical region, and in this case, humans in are the source and main reservoir of infection. Thus, MRSA in companion animals is a humaniosis, which implies that humans are the main reservoir.

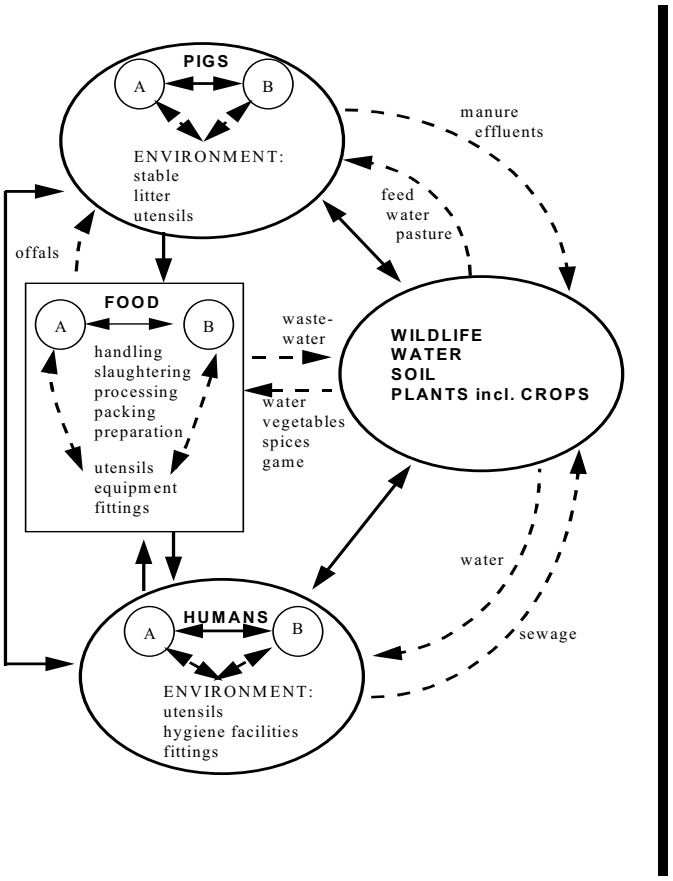

Figure 1. Potential vehicles and routes of spread of antimicrobial resistance (bacteria or resistance genes)

Spread of genes

Another example of extensive gene flux is the emergence and spread of the vanA-gene cluster, coding for vancomycin resistance, is an example of putative zoonotic and pandemic spread of a resistance-genes. Vancomycin and other glycopeptide antibiotics are used for treatment of hospital acquired infections with multiply resistant enterococci or staphylococci. In animal production a related molecule, avoparcin, was used for growth promoting purposes in the EU.

Vancomycin resistant enterococci (VRE) harbouring the *van*A gene cluster have been isolated from humans, both in hospitals and community, from pig, rabbit, dog, cat, horse chicken, turkey, pheasant, duck, food of animal origin and sewage. Through use of modern techniques the phylogenetic relationships of this gene cluster in bacteria isolated from various host species in different countries it has been shown on a number of occasions that strains of VRE from different animal species and humans are generally not related, but they can contain indistinguishable genetic elements coding for resistance.

Containing resistance

Tackling the problems of resistance requires a multidisciplinary approach. Action needs to be taken in all fields where antibiotics are used and professionals need to work in close co-operation. The WHO, among others, has issued recommendations on the containment of antibiotic resistance in different sectors.

Some key elements of an overall strategy are prudent use of antibiotics, education and research and monitoring of use and resistance. Control of infectious diseases will contribute to reducing the need for antibiotics – and to reduce spread of resistant bacteria - and is therefore an important part of a long-term strategy.

Antibiotic treatment during pregnancy and breast feeding

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There is a substantial need for antibiotics in fertile women and, thus, there is also a need to tailor treatment so that it does not cause harm to a foetus if given in early pregnancy. Despite the fact that many antibiotics have been used for decades, current knowledge on their effects on the foetus and neonate is still often limited. By use of the Medical Birth Registry, in which foetal malformations and other neonatal outcomes as well as exposure to medicines in early pregnancy are reported, we have access to a powerful means for surveillance and signal detection. The presentation will discuss use of antibiotics in early pregnancy and neonatal outcome and based on current evidence support some recommendations.

Antimicrobial prophylaxis in surgical and nonsurgical patients

Gunilla Goscinski

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Antimicrobial resistance and STRAMA

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Strama, the Swedish strategic programme against antibiotic resistance, was founded in 1995 as a result of discussions between the Swedish Reference Group for Antibiotics (SRGA), the Medical Products Agency, the National Board of Health and Welfare, the Swedish Institute for Infectious Disease Control, and others. The primary objective was to create a decentralized organization in order to facilitate local surveillance activities and projects concerned with antibiotic use and antibiotic resistance, and it has been supported economically by the Swedish Government since 2000. In September 2006, Strama was reorganized to become a collaborative body working with issues related to effective use of antibiotics in both human and veterinary bacterial infections. A short review of the local Strama activities in connection with a major clonal outbreak of multiresistant *Klebsiella pneumoniae* at Uppsala University Hospital will be given, together with a survey of possible future problems related to multiresistant bacteria.

Strategies against antimicrobial resistance – Strama VL

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The core elements of the Swedish strategy against antimicrobial resistance are illustrated in Figure 1. The strategy involves both human and veterinary medicine, and the basic elements are the same.

Experience from Sweden – both human and veterinary medicine - and other countries shows that effective strategies against antimicrobial resistance should be multifaceted. The main components are monitoring of use and resistance, prevention and infection control, and prudent use of antimicrobials. Continuous information, education and research in all these areas are key to increase awareness and bridge knowledge gaps. Resistance is a global problem impacting on both public and animal health, and it is therefore essential that countries work together and share experiences. Lastly, for these activities to be fully to be effective, a platform for exchange of experiences, collaboration and coordination is needed.

In human medicine in Sweden, the coordinating function is filled by Strama (www.strama.se). During 2008, a secretariat to support a similar organization, Strama VL (VL stands for veterinary and food), has been operative at the National Veterinary Institute (SVA). Its tasks are to coordinate activities aiming to contain antibiotic resistance within the veterinary and food sector, to be and to take initiatives in prioritized areas. Further, as in human medicine Strama VL will actively work to increase awareness of the problems and the possible solutions. Strama VL has been mandated by the Swedish Government, and works in close collaboration with Strama.

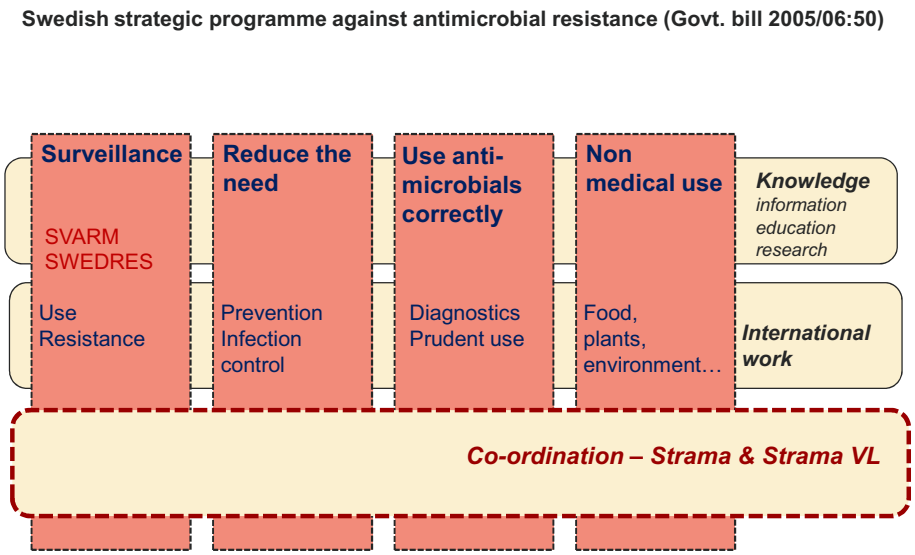

Figure 1. Core elements of the Swedish strategy on antimicrobial re

Handling of an outbreak
A presentation of practical work and experience of the first outbreak of MRSA in a Swedish equine hospital

Karin Bergström

Department of animal health and antimicrobial strategies, National Veterinary Institute (SVA), Uppsala

Introduction:

Outbreak of infectious diseases within the veterinary field can roughly be divided in two categories. One is outbreak of epizootic diseases which can put at risk the total meat production in an area. They are notifiable at suspicion, regulated by law (SFS nr: 1999:6579, SJVFS 199:102/K4) and have emergency service round the clock. The second category, also notifiable (SJVFS 199:102/K4), has less impact to animal and society compared to the epizooties. In this group one can find methicillin resistant *Staphylococcus aureus* (MRSA), notifiable since 1st of January 2008. MRSA has been found in horses and other animal species for quite some time, although Sweden has been "free" until lately. During 2007 one horse was found positive in a study.

MRSA outbreak in an equine hospital:

In May 2008 an outbreak of MRSA at the Uppsala Equine University Clinic was noted. Six horses conducted postoperative wound infections with MRSA. No plan how to deal with an outbreak was established at the clinic. General approval of hygiene and antibiotic policy was in progress since earlier but went slowly because of low priority. At first, both the clinic and authorities needed some time to collect their forces as this is a newly notifiable disease and it happened during the time of year when people comes and goes because of vacation. Knowhow had to be gathered from publications and experience from outbreaks of MRSA in horses at the University Clinic in Helsinki, Finland as well as from a Guelph, Canada. Human health knowledge was also involved and translated to the environmental condition at an equine clinic.

An outbreak of MRSA in animals is also a danger to the people handling the animals. The Swedish Work Environment Authority, the local public human health infection disease control and Previa were therefore highly involved in the outbreak.

All isolates were of the same type; CC (ST) 398, *spa*-type t011, PVL negative. The clone 398 is rather commonly found in swine, calves and horses in some European countries.

What did we learn?

- In outbreaks of resistant bacteria in animals the same concept, although slightly adjusted, as in human health care associated infections can be applied.
- Hygiene, hygiene and hygiene!
- Antibiotic policy!
- Attitude! The work has to be approved all the way from the top to the bottom of the hierarchy.
- The postoperative wound infections in this outbreak healed without antibiotics!

Antimicrobial strategies – asymptomatic bacteriuria / UTI in pregnant women

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As early as in the first trimester progesterone lowers the tone of the bladder and ureters. In the second trimester the uterus and blood vessels mechanically affect the uterers. These physiological changes results in an increased volume of the ureters.

Asymptomatic bacteriuria together with the physiological changes of pregnancy is associated with an increased risk of pyelonephritis with 20-40%. Pyelonephritis in pregnancy can result in premature labour and imply a significant risk for the woman. The risk for miscarriage and prematurity has not been verified in later studies, probably because of early detection and treatment. Asymptomatic bacteriuria, defined as two positive cultures (≥ 100 000 cfu/mL) with at least a couple of days' interval with the same agent, should be treated as a cystitis in pregnant women in contrast to non-pregnant. Women with diabetes or previous cystitis are screened for bacteriuria in Sweden.

Cystitis occurs in 1-2% of all pregnancies, nearly always as a new infection and not resulting from asymptomatic bacteriuria. It is known that 10-20 % get asymptomatic bacteriuria after the cystitis, why urine culture should be performed repeatedly during the rest of the pregnancy.

Antibiotic prophylaxis is given to all women with persistent asymptomatic bacteriuria, after ≥ 2 cystitis and after one pyelonephritis.

E. coli and Staphylococcus saprophyticus are the two primary pathogens, E. coli constitute 80 % of the urinary tract infections in women in reproductive age. Other gram-negative bacteria can also be found. Group B Streptococci can give cystitis in pregnancy.

Antibiotics: Nitrofurantoin and Pivmecillinam are the first drugs of choice for asymptomatic bacteriuria or cystitis in pregnant women in Sweden. Nitrofurantoin is avoided the weeks before delivery and the first month of breastfeeding because of the risk for haemolytic anaemia in children with glucose-6-phosphatedehydrogenase deficit (G6PD). Cephadroxil and Trimethoprim are second choices. Trimethoprim can affect the fetal folic acid metabolism and is not used during the first trimester. Resistance is an increasing problem why Trimethoprim is only used after urine culture.

Pregnant women with pyelonephritis are treated in hospital with Cefotaxime or Piperacillin and Tazobactam intravenously. Gentamycin is added in septic patients.

When antibiotic prophylaxis is indicated Nitrofurantoin or Cephadroxil is used.

Ref: Bergström M, Thomassen P. Okomplicerad UVI under graviditet – diagnostik, behandling och uppföljning. Information från Läkemedelsverket 2:2007.

Antimicrobial strategies – endometritis in cattle

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For optimisation of milk and meat production, a cow needs to give birth once yearly. Uterus needs to be involuted and cyclicity resumed making it possible to start rebreeding the cow at 50-60 days postpartum. In connection to parturition, bacteria invade the female genital tract. The degree of invasion depends on predisposing factors, e.g. sanitary conditions in the calving pen, dystocia, calving assistance, retained foetal membranes and the mother's body condition with over-conditioned cows being more susceptible to disorders. Common bacteria are *Fusobacterium necrophorum, Arcanobacterium pyogenes, Eschericia coli* and *Streptococcus spp*. The histological diagnosis is endometritis, although with very strong self-curing tendency. Most cows spontaneously eliminate bacteria from the uterus within 5 weeks after parturition - without treatment. Cows with retained foetal membranes need some additional weeks for normalisation. The prevalence of endometritis in Sweden is very low, <1%. In individual herds with higher frequencies, prevention and a regular herd health programs are considered the most effective measures. A new policy document for antimicrobial treatment of pigs and cattle will be launched by the Swedish Society of Veterinary Medicine during 2009, where the following treatments for different degrees of endometritis are suggested:

Acute metritis is a serious infection involving deeper layers of the uterus: endometrium, submucosa, muscularis and serosa. It occurs during the first week postpartum. The cow has systemic symptoms (depression, loss of appetite, general weakness and fever >39.5˚C) and often reddish, foetid vaginal discharge. The condition may be fatal if not treated.

Treatment: Systemic treatment with antibiotics is applied in combination with fluid therapy and NSAID. Even though both gram-positive and -negative bacteria usually are present, benzylpenicillin is the drug of choice in Sweden, in most cases with good effect. Broad spectrum antibiotics, tetracyclines, are used if penicillin is ineffective, or as first choice in herds with bacteriological flora known not to respond to penicillin.

Endometritis is a more superficial infection in the endometrium characterised by cattharal-purulent-mucopurulent vaginal discharge that has not ceased 4 weeks after parturition. At palpation via rectum, the uterus is normal (1st degree) or flaccid and enlarged with thickened wall (2nd degree). The cow does not display systemic symptoms of disease, and may even have normal, regular or sometimes irregular cyclicity.

Treatment: Knowledge about therapeutic effect of treatment is lacking, and treatment policies vary greatly between countries. However, from a scientific viewpoint, it can be concluded that antibiotics have a very limited effect on endometritis and there is no general indication for treatment. Instead, the self-healing process should be optimised by supporting treatment. Since oestrus is beneficial for healing, prostaglandin-induced oestrus is an alternative. Swedish dairy and meat farmers' organisations demand a restrictive use of antibiotics; only when apparent indications are present. Therefore, antimicrobial treatment is not indicated in

cases of endometritis without systemic symptoms. Cases with duration longer than 4 weeks postpartum with presence of abnormal vaginal discharge are treated with prostaglandins, a treatment that may be iterated after 10-14 days.

Pyometra (3^{rd} degree endometritis) is characterised by purulent uterine contents, most often closed cervix and no general symptoms of disease. The cow is acyclic with a persistent corpus luteum.

Treatment: Prostaglandin ($PGF_{2\alpha}$) treatment stimulates expelling of uterine contents. The prognosis is very good and antimicrobial treatment is never applied.

Antimicrobial strategies – canine endometritis and pyometra

Ragnvi Hagman

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Pyometra is a serious and potentially life-threatening disease and should always be monitored and managed accordingly [1]. The disease is characterized by metoestral uterine bacterial infection and inflammation resulting in a pus-filled dilated uterus and systemic signs of illness. The most commonly isolated causative bacteria are Gram-negative, with predominance of *Escherichia coli (E. coli)*[2,3]. The safest and most effective treatment is surgical ovariohysterectomy (OHE). In female dogs intended for breeding and that have relatively unaffected general condition and patent cervix, medical treatment may be an option. The strategy for antimicrobial treatment differs depending on treatment method (surgical or medical). It is important to be aware of that antimicrobial treatment causes bacteriolysis with release of bacterial endotoxin into the circulation, and free endotoxin may induce immediate or late detrimental inflammatory effects [4,5].

Surgical treatment of pyometra

Based on the occurrence of post-operative infections, routine pre-operative antimicrobial treatment to all female dogs operated for pyometra is not indicated[6]. The surgical treatment removes the source of infection. Pre-operative antimicrobial treatment is indicated in patients with suspected sepsis, systemic inflammatory response syndrome (SIRS), hypoperfusion or shock, to prevent a fatal outcome [7]. Such patients are identified after physical examination, radiographic or ultrasonographic examination of the uterus and abdomen, laboratory analyses of blood samples determining organ functions, presence of concurrent disease and severity of the systemic inflammation as judged by clinical, inflammatory, haematology and biochemistry parameters [8]. Before surgery the patient's fluid and electrolyte status is evaluated and corrected and as soon as the general condition is stabilised, surgery is performed. If complications likely to progress to sepsis such as uterine rupture during peritonitis are identified, antimicrobial treatment is indicated. The duration of the antimicrobial therapy depends mainly of results from clinical score assessments and close monitoring of the patient during surgery and post-operatively, and should be discontinued accordingly.

The choice of antimicrobial therapy should ideally be determined after bacterial culture and sensitivity testing. Pending the results of culture, antimicrobials effective towards Gram-negative infection is selected in pyometra patients. Importantly, the antimicrobial sensitivity of *E. coli* isolates from female dogs with pyometra in Sweden is favourable compared with what is observed in many other countries [3]. When applying a restrictive policy regarding antimicrobial therapy it is important to inform the dog-owners of early clinical signs indicative of postoperative infection and that they are aware of the urgency of immediate veterinary care if such complications occur. Other factors than the pyometra that are associated with increased risk of infection (host factors, pre-operative factors and factors during surgery such as long duration of the procedure) should be considered in risk assessment of post-operative infection[9]. Wound infections post-operatively are associated with Gram-positive and anaerobic bacteria, and should if necessary be treated with

appropriate debridement and drainage in conjunction antimicrobials (based on bacterial culture and sensitivity testing)[9].

Medical treatment of pyometra

Medical treatment of pyometra always includes antimicrobials as part of the treatment protocol[10-12]. The antimicrobial therapy should be selected after bacterial culture from the cranial vagina, and antimicrobial sensitivity testing. It is also important to consider drug pharmacokinetics and select antimicrobials effective in a pus-filled uterus. The antimicrobial therapy is continued until vaginal discharge is absent or the uterus is ultrasonographically normal, which may last 28 days or more.

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Group B Streptococcus infection in human obstetrics

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Today, GBS have been identified as the most common cause of severe bacterial infection in neonates. The most common serotypes leading to neonatal infections are Ia, III, V, Ib and II The incident of GBS varies in different studies between 0,2 to 2 cases /1000 live born babies.

The bacteria are normally found in the vagina and /or lower intestines in 20 –30% of all pregnant women. Most often GBS colonize the baby during labor either by passing through the cervix upward to the amniotic fluid and the baby or as the infant passes through the birth canal. Early onset GBS infection occurs during the first week of life and can lead to shock, pneumonia and/or sepsis. The majority of the cases – 90 % – will occur during the first 72 hours and the majority already in the first 24 hours.

In a GBS colonized woman there are some high risk situations that substantially will increase the risk of infection in the neonate. These high risk situations are; premature labor (< 37 weeks) rupture of membranes >18 hours before start of labor, maternal fever (> 38 C), a history of child born with severe GBS infection in a previous pregnancy. More that 50% of children getting infected have one of the risk factors present while the remaining have no risk factor present. The mortality among neonates is 5% and higher among premature infants.

The vertical transmission of GBS from mother to baby during labor and the infant getting the infection can drastically be reduced by intrapartum antibiotic administration.

There are different strategies to reduce the neonatal GBS infections such as the screening strategy where all pregnant women are screened in pregnancy week 35-37 and treated during delivery, and the risk based strategy where only women with risk factors will be treated intrapartum.

In Sweden the risk based strategy is recommended after a national study on risk factors for mother and infant colonisation was undertaken 2005. A population-based national cohort of parturients and their infants was investigated A total of 1569 mother/infant pairs with bacterial and obstetric data were obtained. Maternal carriage rate was 25,4%. In GBS positive mothers with no intrapartum antibiotics and vaginal delivery, the infant colonisation rate was 68%, and 30% of infants were colonised after acute caesarian section and 0% after elective CS. The most common serotypes were type III and V. Some 5 % of the isolates were resistent to clindamycin and erytromycin, respectively.

If the screening strategy had been used, more that 30 % of the whole cohort would have received antibiotics versus 22 % of the cohort with the risk based approach.

A screening strategy could cause resistance and a shift in causative agents of neonatal neonatal invasive disease because of liberal use of antibiotics.

Strategies to reduce prevalence of genital Chlamydia in humans

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Between 1988 and 1994, the prevalence of Chlamydia decreased by 62% in Sweden, a trend that, however, eventually gave way in 1995. After 1995, the prevalence of Chlamydia increased each year, reaching the same level in 2005 as in 1988. The decrease in Chlamydia, which was observed after 1988, took place at the same time that large campaigns for safer sex were in progress because of the risk of HIV. The changes in sexual behaviour to fewer sexual partners that took place during this period were due to the acute awareness of HIV infection. When the fear of HIV diminished once it became obvious that there was no spread of HIV in the general population, as had been confirmed by the vigorous testing in Sweden, a reverse trend was observed.

The Swedish strategy to combat Chlamydia is based on extensive screening of young women and partner intervention, where all testing and treatment are free of charge.

To develop a more effective screening strategy, it is important to define persons at risk.

Although the importance of targeting high-risk persons has been extensively discussed, the difficulty still lies in defining these groups. Persons with a prior notification for Chlamydia infection or patients attending sexually transmitted disease clinics could be such a group. An investigation in Stockholm showed that the incidence of Chlamydia increased with the number of sexual partners from 4% with one partner to 12 % with more than one partner during the past 12 months. Among 1000 Chlamydia cases in Stockholm, only 10 % had had more than three partners in the past year. This might be the promiscuous 10%, a group of people that has multiple sexual partners and that fuel the spread of the disease. Most screening activities have been directed toward women but asymptomatic infections among men will probably contribute significantly in sustaining the spread of the infection. It has been assumed that the prevalence of Chlamydia is lower in men than in women but several European studies have shown that Chlamydia prevalence in men was higher than in women.

When screening for Chlamydia by means of home-obtained urine samples, the mailing approach has been shown to be the most efficient strategy for men and high-risk groups, that otherwise are difficult to reach. The mailing strategy has also been shown to be more effective for partner notification.

Large efforts have been directed toward the calling of partners and contact tracing in Sweden. If successful, the partner turns up for testing and treatment. Partner intervention provides an opportunity to break chains of transmission and, moreover, to advise on how to prevent future infections. However, contact tracing has not always proven successful. For instance, the time interval from calling partners, testing and treatment can be considerable.

If Chlamydia infections are to be effectively controlled, new strategies need to be adopted.

A screening strategy that includes men and selective screening of high-risk groups will be necessary in order to decrease the prevalence of Chlamydia in the general population.

The requirement to interrupt transmission of Chlamydia in the population is that the reproductive rate is less than 1, which indicates that every infected individual infects less than one person: with a reproductive rate that is more than one, the epidemic increases. This requirement indicates that enough partners to the index patient have to be traced and treated within a short time to interrupt transmission.

However, the most effective strategy to decrease the Chlamydia incidence is a behavioral change to fewer sexual partners. This reduction in sexual partners occurred in the beginning of 1990s because of the fear of acquiring HIV. In fact, during this period, Chlamydia cases decreased by more than 50%.

Antimicrobial strategies – human mastitis

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Lactation mastitis is a cellulitis of the interlobular connective tissue within the mammary gland. Mastitis seldom occurs within the first 10 days after delivery.

The clinical symptoms range from focal inflammation with minimal systemic symptoms to abscess and septicaemia. The signs and symptoms include fever of 38.5°C or greater; flu-like aches and chills; and a red, tender, hot, swollen, wedge-shaped area of the breast.

The agents most frequently cultured are *Staphylococcus aureus* or *coagulase-negative staphylococci* but also *group B Streptococci* occur. Several different agents could also be found in one case.

There are few formal studies on mastitis in humans. Several investigators suggest a fissure in the nipple as a route of infection Risk factors fall into two general categories: poor breastfeeding technique and lowered immune status secondary to stress and sleep deprivation. Poor breastfeeding technique may lead to poor drainage of a duct, insufficient emptying of the breast, milk stasis, and cracks or fissures of the nipple.

A challenge is to separate an infectious mastitis from the inflammatory response to milk stasis, which could also give flu-like symptoms as high fever, chills, aches, and elevated white blood cell count and CRP. To empty the breast by breastfeeding, manual milking or with a mechanical pump is the most important treatment. If the symptoms do no not resolve within two days, antibiotics should be considered. In Sweden *Flucloxacillin* is the first choice, if only group B streptococci are found in the culture *Phenoximethylpenicillin* could be used. *Clindamycin* is the second choice.

Abscesses are reported to occur in 11 percent of all affected women. Ultrasound is used for detection and drainage with pigtail catheters.

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Antimicrobial strategies – mastitis in cattle

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Mastitis is the most common disease in dairy cows. Every year approximately 15-20% of the cows in Sweden are treated for mastitis by a veterinarian. Most of those are clinical cases, and treatment often includes the use of antimicrobials. In Sweden it is estimated that 70% of all treatments with antimicrobials in cattle are due to mastitis. Veterinary policy for prudent use of antimicrobials in mastitis are therefore of great importance. The first policy was introduced 1995 and the latest update will be presented in 2009. Important parts of the policy are to use antimicrobials only in selected cases, base the use on bacteriological diagnosis, use narrow spectrum drugs and evaluate the outcome of the treatment. Thus, it is normally not recommended to use antimicrobials if the prognosis is poor for example in chronic cases. In cases with good prognosis it is, however, important to start treatment with antimicrobials as quickly as possible. The choice of antimicrobial should be based on bacteriological examination of milk samples. In Sweden, most cases of mastitis are caused by penicillin sensitive staphylococci or streptococci. Benzyl penicillin is therefore the first drug of choice in most cases. In clinical mastitis systemic administration (mostly intramuscular injections) is recommended when antimicrobials are used. The importance of using a correct dose and duration of treatment is emphasized. In all cases symptomatic treatment, e.g. NSAID and/or fluids, should be given when needed, and the farmer should be advised on how to take care of the animal. In addition, recommendations on preventive measures to avoid spread of udder infections within the herd should be given.

Antimicrobial strategies in Artificial insemination

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A prerequisite for artificial insemination (AI) is storage of semen outside the body (i.e. to prolong the fertile life of the spermatozoa) for a certain time to be able to circumvent geographical limitations as well as differences in time between males and females. Therefore, the collected semen must be diluted in an appropriate extender which, among other functions, must provide an effective antibiotic treatment of the semen to be inseminated. The aim is to reduce or inhibit the growth of microorganisms arising from an unavoidable preputial contamination of the collected semen. Different types of antibiotics are used for different extenders and different species. Earlier penicillin and streptomycin were used, but today antibiotics with a broader spectrum such as gentamycin, lincomycin, and spectinomycin, and fungicides like amphotericin B, are routinely added to commercial semen extenders.

The volume of the insemination dose as well as the number of AIs used per heat varies considerably between species e.g. the volume for AI in horses and pigs varies roughly between 20 to 80 ml/dose and this dose is deposited 2-3 times per heat, resulting in a large volume and a relatively high amount of antibiotics being deposited in total. Increased amounts of antibiotics are being added to the extenders nowadays to enable a longer durability of the extended semen doses, but no studies regarding the de-escalation of the effect of different types of antibiotics during storage have been reported. Only studies regarding the effect of different types of antibiotics on the viability of spermatozoa during storage are found in the literature. Furthermore, virtually nothing seems to be known about the degree of resorption of the antibiotics after deposition in the female genital tract and subsequent development resistance by microorganisms. Should a with-holding period for milk or meat be given for females subjected to AI? Finally, we also tend to neglect that a certain amount of the volume of the AI-dose often comes out due to back flow after AI, but nothing is reported about the effect these antibiotics have on the environment once they are shed on the floor, mixed with faeces and passes out into circulation. Resistant bacteria in AI-doses from boars are becoming a growing problem, not just in the US, but also in southern parts of the EU.

The extent of AI worldwide is considerable with many hundreds of millions of females being inseminated annually. Therefore careful antimicrobial strategies in AI ought to be developed speedily to minimise the risk for development of resistance. Furthermore, clear recommendations need to be made on how to best destroy surplus extended semen and surplus extender.

Antimicrobial strategies - mating and AI in horses

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Modern horse reproduction is based on the use of artificial insemination. Swedish Warmbloods and Standardbred trotters are the breeds in Sweden with the highest number of mares mated per year, for 2008 approximately 5300 and 5000, respectively. In these two breeds there has been a steady increase during the latest 25 years in number of mares being inseminated compared with natural mating. In 2008 approximately 95% of the mares were inseminated. Insemination can be made either with fresh, chilled or frozen semen. Insemination with chilled semen has been very popular in the Swedish Warmbloods because chilled semen doses can be transported. Last year chilled semen was used in approximately 65% of the inseminated Warmblood mares.

Semen for insemination is diluted in an extender which contains antibiotics. The final volume per semen dose is in most cases 20 ml and the amount of extender varies depending on the sperm concentration (ejaculate:extender, 1:1 – 1: 4). Kenney's extender (Kenney et al., 1975) has for many years been the standard extender used. It contains penicillin (150.000 IU/100 ml) and streptomycin (150 mg/100 ml). However, since it is in dry form and has to be dissolved in sterile water prior to use, commercial "ready to use extenders" have become popular. One commercial extender that nowadays is dominating at Swedish studs is INRA-96 (produced by IMV technologies under licence from INRA). This extender contains penicillin, gentamicin and the fungicide Amphotericin B. However, information about the amount of antibiotics added is not available. Since semen extenders contain antibiotics, mares receive a low dose of intrauterine antibiotics at insemination. If this low dose of antibiotics may disturb the normal bacteria flora in vestibulum/vagina and thereby increase the risk of multi resistance is not known but will be studied coming summer in a pilot study.

All mares get an acute inflammatory reaction in their endometrium after insemination due to sperms being allogeneic, i.e. foreign to the mare. This reaction is physiological and normally temporary. In healthy mares, the uterus is cleared within two days. However, in some mares, especially older mares, the endometritis may persist due to fluid accumulation. Earlier, these "sensitive mares" were often treated with intrauterine antibiotics after mating. Nowadays, the post mating therapy is to assist the mares with fluid accumulation so they can clear their uterus, either by injecting oxytocin to stimulate uterine contraction, mechanically evacuate the fluid with uterine saline lavage or use a combination of both these treatments.

In other cases with fluid accumulation in the uterus, i.e. endometritis, diagnosed by discharge and/or ultrasound, uterine samples for bacteriological culture and resistance pattern should be taken before deciding about antibiotic therapy. The most commonly isolated bacteria in mares with endometritis are *Streptococcus equi ssp zooepidemicus* and *E. coli*. Also in these cases treatment should start with uterine saline lavage before the administration of antibiotics. If intrauterine antibiotic is to be given, the choice is important since some type of antibiotics are very irritant to the endometrium.

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