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Assessment of the transfer of antimicrobial resistance between pets and humans in Norway

Opinion of the Panel on Biological hazards of the Norwegian Scientific Committee for Food Safety

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Assessment of the transfer of antimicrobial resistance between pets and humans in Norway

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Assessed and approved

The opinion has been assessed and approved by the Panel on Biological Hazards of VKM. Members of the panel are: Yngvild Wasteson (chair), Karl Eckner, Georg Kapperud, Jørgen Lassen, Judith Narvhus, Truls Nesbakken, Lucy Robertson, Jan Thomas Rosnes, Taran Skjerdal, Eystein Skjerve, Line Vold, Siamak Yazdankhah

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

In 2014, the Norwegian Food Safety Authority (NFSA) requested an assessment on the transfer of antimicrobial resistance (AMR) between pets and humans from VKM. VKM appointed a working group consisting of members of the Panel on Biological Hazards and one external expert to prepare the answers to the questions posed in the Terms of Reference (ToR). One member from the Panel on Animal Health and Welfare contributed as a hearing expert. The Panel on Biological Hazards has reviewed and revised the draft prepared by the working group, and the assessment has been adopted.

AMR can be described as the ability of a bacterium to withstand the effects of an antimicrobial (Abbreviations and glossary).

Resistance to antimicrobial agents may be intrinsic or acquired. Intrinsic resistance is a natural property of an organism resulting in decreased susceptibility to a particular antimicrobial, whereas acquired resistance is a result of genetic changes in an organism due to mutation or the acquisition of extra-chromosomal genetic material.

AMR is a major threat to human health; not only is it a threat to the control of bacterial diseases, but it is also a threat to modern medicine in general. To date, AMR has been described for all known antimicrobials currently available for clinical use. Use of antimicrobials inevitably has resistance development as a side effect, and therefore all categories of antimicrobial use should be evaluated, including use of antimicrobials for humans, production animals, companion animals, and plants.

Increasing amounts of antimicrobials are used for treatment of pets, including numerous substances used in human medicine. The main bacteria of concern include *Staphylococcus pseudintermedius* and *Escherichia coli*, as well as other organisms of clinical importance in human medicine, such as methicillin-resistant *Staphylococcus aureus* and *Enterobacteriaceae* spp. Transmission of such organisms occurs between pets, owners, and veterinary staff. Pets can act as reservoirs of these bacteria and their occurrence can impact on the use of antimicrobials in human medicine.

An increase in sales of antimicrobials marketed for companion animals of 19 % was observed in Norway between 1995 and 2014. This increase was mainly accounted for by penicillins, and approximately 87 % of the penicillin products sold for use in companion animals during 2014 was as a combination of amoxicillin and clavulanic acid.

According to the Norwegian monitoring programme for AMR in the veterinary sector, the frequency of resistance reported in pet animals has been stable since the start of the programme in the year 2000.

The nature of relationships between pet animals and their owners has changed considerably during the last decades, and today many pet animals commonly live as family members in

the household in close contact with their owners. Interspecies transmission (in both directions) between pets and humans, and between pets and other animal species, can occur by direct contact or indirectly through environmental contamination of households, veterinary clinics, and public spaces.

In recent years, an increasing number of pet owners have become interested in feeding raw meat or fish to their pet dogs rather than commercial dry food. The increasing occurrence of AMR in bacteria in food-producing animals in Europe, and to a certain extent in Norway, means that raw meat provided to Norwegian dogs as feed represents a close contact between dogs and the domestic pool of AMR in Norwegian livestock and, to a certain extent, the international population of domestic animals.

Today's travel with animals and relatively unregulated import, especially of dogs, exemplifies an open population. In addition, many dogs also travel, mainly inside the EU/ EEA due to the relaxation of regulations. Travel to areas with high endemic levels of bacteria with AMR has been indicated as a risk factor for the acquisition of such bacteria. Most studies have been conducted on human travellers, but there is no reason to believe that the microbiota of pets behave differently.

This means that the Norwegian dog population is in contact with the whole European population of dogs, with the long-term effect that the Norwegian human population will also be exposed to AMR patterns introduced to Norway by travelling dogs and dogs imported from other countries.

Probability characterization – answers to the questions

- According to current knowledge *S. aureus*, *S. pseudintermedius,* and *Enterobacteriaceae* spp. are the bacteria of most concern regarding transfer of AMR directly between pets and humans. However, the literature is limited and evidence indicating the specific bacteria most likely to transfer resistance directly or indirectly between pets and humans is lacking.
- Broad-spectrum antimicrobials, such as cephalosporins and fluoroquinolones, are traditionally associated with promotion of resistance. The extensive use of amoxicillin and clavulanic acid can promote the same type of resistance as cephalosporins. In addition, it is also known that even narrow-spectrum antimicrobials, such as phenoxymethylpenicillin, may induce and promote resistance in bacteria.
- The register of prescriptions available to NFSA, issued by veterinarians and dispensed by pharmacies, was established earlier, but not all pharmacies participated in the register before 2015. It is thus currently impossible to extract reliable data on real consumption of human medicinal products (HMP) and veterinary medicinal products (VMP) in pet populations and to establish the extent to which antimicrobial drugs are used for pets.
- The following factors have been identified as being likely to increase the development and dissemination of AMR to such an extent that the probability for direct or indirect

transfer of AMR between pets and humans in Norway should be regarded as non-negligible:
    - Use of antimicrobials.
    - Therapeutic use of antimicrobials in the Norwegian dog and cat populations.
    - The Norwegian dog population being part of an open population with extensive international contacts.
    - Use of raw pet food of animal origin.
- Minimal veterinary use of critically important antimicrobials (CIA) licensed for human use only should reduce the development of the resistance to those antimicrobials.
- Guidelines and education about the zoonotic risks associated with household pets can help to reduce the probability of transfer of AMR. Low awareness of primary healthcare practitioners about zoonoses transmitted by pet animals, and communication difficulties between veterinary and medical practitioners can lead to less timely diagnoses and identification of resistant strains. Providing sufficient space and attention to companion animal zoonoses in medical and veterinary university curricula, as well as in continuing education, can raise awareness and identify possible emerging resistant strains.
- Clear diagnostic routines and reporting lines can lead to the development of a clearer picture on the existing prevalence of resistance in pet populations, and also provide information on possible pathways for spreading.

Key words: VKM, assessment, Norwegian Scientific Committee for Food Safety, Norwegian Food Safety Authority/Norwegian Environment Agency, pets, antimicrobial resistance

Sammendrag på norsk

I 2014 bestilte Mattilsynet fra Vitenskapskomiteen for mattrygghet (VKM) en vurdering av overføring av antimikrobiell resistens mellom dyr og mennesker. VKM nedsatte en prosjektgruppegruppe bestående av medlemmer av Faggruppen for hygiene og smittestoffer og en ekstern ekspert til å forberede svar på spørsmålene fra Mattilsynet. Ett medlem fra Faggruppen for dyrehelse og dyrevelferd har bidratt som en høringsekspert. Faggruppe for hygiene og smittestoffer har gjennomgått og vurdert utkast utarbeidet av prosjektgruppen, og godkjent vurderingen.

Antimikrobiell resistens kan beskrives som evnen til en bakterie til å motstå virkningen av et antimikrobielt stoff. (Forkortelser og ordliste)

Resistens mot antimikrobielle midler kan være iboende eller ervervet. Iboende resistens er en naturlig forekommende egenskap som fører til nedsatt følsomhet overfor et spesielt antimikrobielt stoff. Ervervet resistens kommer som en følge av genetiske endringer på grunn av en mutasjon eller ervervelsen av ekstra-kromosomalt genetisk materialet hos en bakterie.

Antimikrobiell resistens er en stor helsetrussel for mennesker, ikke kun som en trussel mot kontroll av infeksjoner, men også som en trussel mot moderne medisin generelt. Til dags dato har antimikrobiell resistens blitt beskrevet for alle kjente antimikrobielle stoffer tilgjengelige for klinisk bruk. All bruk av antimikrobielle stoffer har resistensutvikling som en bivirkning, og derfor alle kategorier av antimikrobielle stoffer i bruk må vurderes. Dette inkluderer bruk av antimikrobielle midler til mennesker, til produksjonsdyr, til kjæledyr og planter.

Det brukes stadig mer antibiotika til behadling av dyr, inkludert mange preparater som brukes i humanmedisin. De viktigste resistente bakterier inkluderer *Staphylococcus pseudintermedius* og *Escherichia coli*, så vel som andre organismer av klinisk betydning hos mennesker, slik som meticillinresistente *Staphylococcus aureus* og *Enterobacteriaceae* spp. Disse bakteriene kan overføres mellom kjæledyr, eiere og veterinær. Kjæledyr kan fungere som reservoarer for slike bakterier og deres forekomst kan ha en innvirkning på bruken av antibiotika i humanmedisin.

I perioden 1995-2014 økte salget av antimikrobielle stoffer som markedsføres for kjæledyr i Norge med 19 %. Økningen kan hovedsakelig forklares med økt bruk av penicilliner. I 2014 var ca 87 % av penicillin preparater som selges til bruk til kjæledyr en kombinasjon av amoxicillin og klavulonsyre.

Ifølge Norsk overvåkingssystem for antibiotikaresistens hos mikrober i veterinær sektor (NORMVET) har forekomst av rapportert resistens hos kjæledyr vært stabil siden starten av programmet i 2000.

Mange kjæledyr i dag lever som familiemedlemmer og er i nær kontakt med sine eiere. Overføring av resistens mellom arter) mellom dyr og mennesker, og mellom kjæledyr og andre dyrearter, kan skje ved direkte kontakt eller indirekte gjennom miljøforurensning av husstandene, veterinærklinikker og fellesarealer.

De senere år har stadig flere hundeeiere begynt å mate hundene sine med rå mat istedenfor tørrfôr. Økende forekomst av AMR i matproduserende dyr i Europa og til en viss grad i Norge, fører til en situasjon hvor rå fôret til norske hunder representerer en nær kontakt mellom innenlands pool av AMR i husdyr og hunder. I tillegg øker den også til en viss grad kontakten med den internasjonale pool av AMR hos husdyr.

Dagens regler for reise med dyr og mer eller mindre uregulert innførsel, spesielt av hunder, illustrerer en svært åpen populasjon. Mange hunder reiser, hovedsakelig innenfor EU / EØS på grunn av liberalisering av regelverket. Reiser til geografiske områder der endemiske nivåer av AMR er høye, har vært påpekt som en risikofaktor for å bli smittet av slike bakterier. De fleste studier er gjennomført på reisende mennesker, men det er ingen grunn til å tro at bakterieflora hos kjæledyr overføres forskjellig.

Dette betyr at norsk hundepopulasjon er i kontakt med europeisk hundepopulasjon. Langtidseffekten er at vi blir utsatt også for AMR introdusert til Norge gjennom hunder som reiser og hunder som er innført fra andre land. Vi har begrenset informasjon for hunder, og data om kattene er enda begrenset.

Sannsynlighets karakterisering - svar på spørsmålene

- Det er dokumentert at bakterier *S. aureus*, *S. pseudintermedius* og *Enterobacteriaceae* spp. kan overføre resistens direkte mellom dyr og mennesker. Litteraturen er imidlertid begrenset, og det finnes ingen grunn til å peke på spesifikke mikroorganismer som de mest sannsynlige til å overføre resistens direkte eller indirekte mellom kjæledyr og mennesker.
- Bredspektrede antimikrobielle stoffer som cefalosporiner og fluorokinoloner er tradisjonelt forbundet med utvikling av resistens. Den utstrakte bruken av amoxicillin og klavulonsyre kan fremme den samme type motstand som cefalosporin. I tillegg er det også kjent at selv smalspektret fenoksymetylpenicillin kan fremme utvikling av resistens hos bakterier.
- Registeret over utlevert legemidler etter forskrivning fra veterinær ble etablert tidligere og skal inneholde alt av medisiner som forskrives til kjæledyr. Det er først fra 2015 at de fleste apotekene har rapportert utlevert medisin. Det er derfor, for tiden, ikke mulig å trekke sikre konklusjoner om virkelig forbruk av HMP og VMP i dyrepopulasjoner og å fastslå i hvilken grad antimikrobielle stoffer brukes for kjæledyr.
- det er en ikke-neglisjerbar sannsynlighet, både for direkte og indirekte overføring av resistens for:
    - den totale bruken av antimikrobielle stoffer (mennesker og dyr)
    - terapeutisk bruk hos katter og hunder
    - åpen hund populasjon kontakt

- Minimal veterinær bruk av kritisk viktige antimikrobielle stoffer (CIAs) registrert kun for bruk hos mennesker kan redusere utviklingen av resistens mot de antibiotika.
- Utdanning om zoonotiske risiko forbundet med husdyr kan hjelpe å redusere risikoen for overføring av antimikrobiell resistens. Lav bevissthet hos primærhelsetjenesten om zoonoser som overføres fra kjæledyr og vanskeligheter i kommunikasjon mellom veterinær og leger kan føre til forsinket diagnose og identifisering av resistente stammer. Nødvendig plass og oppmerksomhet gitt til zoonose hos kjæledyr i medisinsk og veterinær utdanning samt i videreutdanning kan bedre bevisstgjøring og identifisering av mulige nye resistente stammer.
- Klare diagnostiske rutiner og rapporteringslinjer kan føre til et klarere bilde av eksisterende forekomst av resistens i kjæledyr befolkningen samt gi informasjon om mulige spredningsveier.

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Abbreviations and glossary

Abbreviations

AMR	Antimicrobial resistance
CIA	Critically important antimicrobial
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
DAG	Direct acyclical graphs
EFSA	European Food Safety Authority
ESBL	Extended-spectrum beta-lactamase
ExPEC	Extra-intestinal pathogenic *E. coli*
HA-MRSA	Hospital-acquired, methicillin-resistant *Staphylococcus aureus*
HGT	Horizontal gene transfer
HMP	Human medicinal products
LA-MRSA	Livestock-associated methicillin-resistant *Staphylococcus aureus*
MDR	Multi drug resistant
MRCoPS	Methicillin-resistant coagulase-positive staphylococci
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSP	Methicillin-resistant *S. pseudintermedius*
MSSP	Methicillin-susceptible *S. pseudintermedius*
NFSA	Norwegian Food Safety Authority
NORM	The Norwegian monitoring programme for AMR in human pathogens
NORM-VET	The Norwegian monitoring programme for AMR in bacteria from food, feed, and animals
ST	Sequence type

VKM	Norwegian Scientific Committee for Food Safety
VMP	Veterinary medicinal products
VRE	Vancomycin-resistant Enterococci
WHO	World Health Organization

Glossary

Acquired resistance: Resistance to a particular antimicrobial agent to which the microorganism was previously susceptible. The change is the result of genetic changes in a microorganism due to mutation(s), the acquisition of foreign genetic material, or a combination of both mechanisms.

Antibiotics: Traditionally, natural organic compounds produced by microorganisms, acting in low concentrations against other bacterial species. Today, “antibiotics” also includes synthetic and semisynthetic compounds with similar effects.

Antimicrobial agents: A general term for the drugs (antibiotics), chemicals, or other substances that either kill or inhibit the growth of microbes. The concept of antimicrobials applies to antibiotics, disinfectants, preservatives, sanitizing agents, and biocidal products in general.

Antimicrobial resistance is defined as (Davison et al., 2000):

1. A property of bacteria that confers the capacity to inactivate or exclude antimicrobials, or a mechanism that blocks the inhibitory or killing effects of antimicrobials.
2. The ability of a microorganism to withstand an antimicrobial.
3. A relative term that provides an interpretation of the clinical significance of concentrations of an antimicrobial that inhibits the growth of an organism or kills it in laboratory systems (*in vitro*).
4. Either microbiological resistance, where resistant organisms are those that possess any kind of resistance mechanism or resistance gene, or clinical resistance, where a bacterium is classified as susceptible or resistant depending on whether an infection with that bacterium responds to therapy or not.

Clone: Bacterial isolates which, although they may have been cultured independently from different sources in different locations and perhaps at different times, still possess so many identical phenotypic and genotypic traits that the most likely explanation for this identity is a common origin within a relevant time span.

Conjugation: Transfer of genetic material between different cells by direct cell-to-cell contact.

Co-resistance: Resistance occuring when the genes specifying different resistant phenotypes are located together on a mobile genetic element (e.g., plasmid, transposon, integron).

Cross-resistance: Resistance occurring when the same or similar mechanism(s) of resistance applies to different antimicrobials.

Indicator bacteria: Bacteria used to measure the hygienic conditions of food, water, processing environments etc. The indicator bacteria are usually not pathogenic themselves, but their presence indicates that the product or environment tested may be contaminated with pathogenic bacteria originating from the same reservoirs as the indicator organisms.

Intrinsic resistance: A natural property of an organism resulting in decreased susceptibility to a particular antimicrobial agent.

Isolate: A bacterial isolate can be defined as a single isolation in pure culture from a specimen.

Selection: A process by which some bacterial species or strains of bacteria within a population are selected for by having a specific advantage over other microorganisms. Antimicrobial transduction substances may provide a more resistant sub-population with such an advantage, thereby enabling them to increase their relative prevalence.

Strain: A subset of a bacterial species differing from other bacteria of the same species by some minor, but identifiable, difference.

Susceptibility: A characteristic that describes the extent to which a target microorganism is affected by an antimicrobial agent.

Transduction: Transfer of genetic material from one bacterium to another via bacteriophages (viruses that infect bacteria and are integrated into the host genome).

Transformation: Direct uptake from the environment of fragments of naked DNA and its incorporation into the cell's own genome.

Background as provided by the Norwegian Food Safety Authority

In recent years there has been a dramatic increase in antimicrobial resistance (AMR) worldwide. Known mechanisms of resistance have increased in scope, and new mechanisms have emerged. This leads to serious consequences in terms of prolonged suffering and increased mortality, and requires enormous use of resources to address these problems. The increasing trade and migration patterns across national borders and continents contribute greatly to this development. Pets travel more than before, and international trade in pets has increased significantly in recent years. The challenge is therefore global, and must be solved through international cooperation and targeted actions. This is challenging, both academically and politically.

In Norway, there are over a million cats and dogs, of which 2/3 are cats and 1/3 dogs. Antimicrobials used to treat infections in dogs and cats are often the same as those used in human medicine, including broad-spectrum antibiotics such as cephalosporins and fluoroquinolones. The use of antibiotics is considered to be a major cause of development and selection of bacteria with AMR. In the past decade, a number of scientific papers from different countries have reported spread from pets to humans of bacteria with AMR.

Resistant bacteria can be transmitted between pets and humans either by direct bacterial infection or indirectly, by resistance genes being transferred between bacteria in companion animals and humans. Examples of bacterial species with special - and sometimes dreaded - resistance patterns that have been isolated from pets and have the potential to colonize humans, include the following (the list is not exhaustive):

Staphylococcus spp.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was, until recently, a rare cause of infections in pets, but detected frequently in cats and dogs.

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) infections are prevalent in cats and dogs, but has also been isolated from humans. MRSP has been isolated both from small animals and humans in Norway.

Enterococcus spp.

Vancomycin-resistant enterococci (VRE) in dogs. Such microbes are greatly feared in human infections because they are difficult to treat.

Streptococcus spp.

Especially *S. canis* in dogs and cats. Resistance to erythromycin, clindamycin, penicillin, trimethoprim/sulphonamide occurs.

Escherichia coli

E. coli that produce extended-spectrum beta-lactamases (ESBL/AmpC) and tetracycline resistance. *E. coli* bacteria in pets can be a significant hazard to public health.

Salmonella spp.

Multi-resistant *Salmonella* bacteria have been isolated from both dogs and cats.

Pseudomonas spp.

The development and spread of bacteria with AMR in pets is increasing, and is considered challenging for both animal health and human health. There is therefore a need for an assessment of transmission of bacteria with AMR between pets and humans and vice versa, and an assessment of the consequences that this may have on public health and animal health in Norway.

Terms of reference as provided by the Norwegian Food Safety Authority

The Scientific Committee for Food Safety (VKM) is requested to consider especially bacteria / resistance forms for which dogs and cats might be thought to represent a special risk as well as a substantial proportion of the total burden that bacteria with AMR inflicts on public health in Norway. This includes assessing whether there are any gaps in knowledge that are important to fill in terms of developing a future strategy for reducing the potential for cats and dogs to act as reservoirs of resistance for humans and livestock. For example, does feeding raw meat to dogs and cats confer a risk of transfer of resistance to humans?

Based on the information above, the NFSA requests an Opinion regarding the following issues:

1. Which bacteria are most likely to transfer AMR between pets and humans (under Norwegian conditions)? Considering both direct and indirect transfer:
    a. Which antimicrobials used in the treatment of dogs and cats are most likely to induce resistance?
    b. Are dogs and cats reservoirs for bacteria that can cause illness and simultaneously transfer resistance? If so, which are these bacteria?
2. To what extent are antimicrobial drugs used for pets? This question applies both to antimicrobial pharmaceuticals indicated for animals and human drugs. Which drugs are being used, how much, and for which indications?
    a. Human medicinal products (HMP).
    b. Veterinary products (VMP).
3. Which risks exist for direct transmission of resistant bacteria between pets and humans under Norwegian conditions?
4. Which risks exist for indirect transfer of resistance genes between pets and humans (under Norwegian conditions) via the respective bacteria?
5. Which of the following risk reduction measures will be most effective at reducing the increase of resistance?
    a. WHO has defined antimicrobials that are critical for human use. Will banning the use of these antimicrobials in the treatment of dogs and cats have any effect?
    b. Guidelines for handling pets with (risk) resistant bacteria (like ones in health care)?
    c. Clarification of the duty of notification upon detection of resistant bacteria.
6. Which bacteria are good indicators for surveillance of resistance in dogs and cats?

1 Literature

1.1 Relevant background papers

- Report on the use of antimicrobials and prevalence of resistance among microorganisms from animals (NORM-VET) in Norway
- Data from the Food Safety Authority's supervision of animal health, etc. (MATS)
- Extracts from registry of prescriptions

1.2 Literature searches performed in PubMed

The following searches in PubMed were performed:

Search: ((((cat*[Title/Abstract]) OR dog*[Title/Abstract]) OR pet[Title/Abstract]) AND antimicrobial[Title/Abstract]) AND resistance[Title/Abstract] Filters: Review – n=32

Search: ((((cat*[Title/Abstract]) OR dog*[Title/Abstract]) OR pet[Title/Abstract]) AND antimicrobial[Title/Abstract]) AND resistance[Title/Abstract] Filters: 10 years, Other Animals – n= 235

Antibiotic resistance dog model - n=50[1]

Antibiotic resistance dog pet - n=11

Antibiotic resistance pet humans - n=51

Antibiotic resistance pet humans - n=326

The following searches in Web of Science were performed:

"Antimicrobial resistance" and "(dog or cat or pet) and "risk assessment: n=371;

"Antimicrobial resistance" and (zoonosis and zoonotic) and (dog or cat or pet) and model; n=861.

1.3 Relevance screening

The titles of all hits were scanned and the abstracts were inspected for those of potential relevance. This screening for relevance was performed independently by the members of the

[1] Models describing what is needed for this risk assessment are scarce among this literature

ad hoc group. Citations were excluded if they did not relate to the ToR. The reference lists in selected citations were examined to identify additional articles or reports that had not been identified in the database searches.

2 Introduction

2.1 Antimicrobial resistance (AMR)

AMR is a major health threat to humans. In clinical medicine, the development of AMR in human pathogens has been widely publicized and is recognized as a major threat to the control of bacterial diseases and infections worldwide (Levy, 1992; WHO, 2011). It has been estimated that 25 000 patients die yearly in Europe from infections caused by antimicrobial resistant microorganisms (WHO, 2011). AMR has been described for all known antimicrobials currently available for clinical use and this development may result in a major public health crisis, threatening the return of untreatable infections on a massive scale.

Increasing amounts of antimicrobials are used in pets, including numerous substances used in human medicine. This is a consequence of the trend towards treating diseases in pets in the same way as in humans, including many chronic diseases for which long-term medication is needed. There is evidence that resistance to antimicrobials is increasing among bacteria that cause infections in pets. These bacteria include *Staphylococcus pseudintermedius* and *Escherichia coli*, as well as other organisms of clinical importance in humans, including methicillin-resistant *S. aureus*. Transmission of such organisms, particularly pathogenic staphylococci, occurs between pets, owners, and veterinary staff, and pets can act as reservoirs of such bacteria. This may have an impact on the use of antimicrobials in human medicine (Cohn and Middleton, 2010; Kadlec and Schwarz, 2012; Lloyd, 2007). While this transfer is well described, the importance of the transfer regarding development and dissemination of AMR, as compared with the importance of drug use in humans or pets, is less explored.

Most studies investigating the risk of transfer of AMR have focused on food-producing animals, as exemplified by the lack of risk assessment reports on this issue in the FoodRisk repository (http://foodrisk.org/). The same lack of reports is demonstrated in the homepages of the European Food Safety Authority (EFSA), where discussion has mainly focused on food-producing animals. The report “EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013” (EFSA/ECDC, 2013) only focuses on food-producing animals.

However, the scientific literature contains a number of publications in which the risk of AMR transfer between humans and pets is discussed (Barber et al., 2003b; Boysen et al., 2014; Evers et al., 2014; Guerra et al., 2014; Hald et al., 2004; Heller et al., 2010a). Qualitative

(Heller et al., 2010b) and quantitative risk models for transfer of bacteria between pets and humans (Evers et al., 2014) are also found. Further, publications on risk-based surveillance (Stark et al., 2006) give hints on how to approach the question of surveillance for AMR. Methods of interest include the much-used source attribution techniques, as used for campylobacteriosis in Denmark (Boysen et al., 2014).

2.2 Classification of antimicrobials according to their importance in human medicine

A paper by of Collignon et al., (2009) gives an overview of the WHO ranking of antimicrobials used in human medicine. This list divides antimicrobial agents used in human medicine into three different categories:

- Critically important antimicrobials (CIA),
- Highly important antimicrobials, and
- Important antimicrobials

For this ranking each antimicrobial agent (or class) was assigned to one of the three categories of importance on the basis of two criteria: (1) the agent or class is the sole therapy or one of few alternatives to treat serious human disease; and (2) the antimicrobial agent or class is used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases caused by organisms that may acquire resistance genes from non-human sources.

Critically important antimicrobials are those that meet both criteria.

Highly important antimicrobials are those that meet one of two criteria.

Important antimicrobials are those that do not meet either criterion.

This list was generated in an effort to provide a tool for developing risk-management strategies and to focus resources to address antimicrobial use in agriculture and veterinary medicine. Prior to this, there had been no international consensus on the classification of different groups of antimicrobial agents. The WHO convened a second meeting in Copenhagen, Denmark in 2007 to re-evaluate the classification of antimicrobials and update the list on the basis of recent developments. Relatively few changes were needed. For further reading, please refer to VKM assessment of antimicrobial resistance in the food-chain (VKM, 2015).

2.3 Antimicrobial agents used in pets

The overview of antimicrobial classes marketed and used for dogs and cats in Norway is given in Appendix I, Table 13-1.

The number of pet animals has increased substantially overall in modern society, and pet welfare is the subject of considerable attention. Antimicrobial agents, including antimicrobial preparations used in human medicine, are frequently used in small animal veterinary practice, including an extensive use of broad-spectrum agents such as aminopenicillins, clavulanic acid, cephalosporins, and fluoroquinolones (defined as critically important in the WHO list). There is no such classification of antimicrobials for use in pets. Several longitudinal studies conducted at veterinary hospitals in different countries have indicated that resistance to various antimicrobial agents has emerged amongst pet animal isolates of *S. pseudintermedius*, *E. coli,* and other bacteria. This includes species with a potential for zoonotic transmission and resistance phenotypes of clinical interest, such as MRSA, VRE, and MDR *Salmonella* Typhimurium DT104. A marked contrast is evident between the current policies on antimicrobial usage in food-producing and companion animals. Apart from a few countries where limited data on antimicrobial usage and occurrence of resistance in bacteria from pet animals have been collated, national surveillance programmes focus only on food-producing animals. The rationale behind this may be the view that the potential consequence of transfer through foods is greater than from pets to humans. However, data on drug use in pet animals are clearly needed for guiding antimicrobial use policies in small animal veterinary practice, as well as for assessing the risk of transmission of AMR to humans (Damborg et al., 2004; Guardabassi et al., 2004a; Guardabassi et al., 2004b). The VKM report (VKM, 2015) gives data on the use of antimicrobials in food-producing animals, while the data for pets are less clear. According to NORM/NORM VET, sales of antimicrobials marketed for companion animals increased by 19 % in Norway in the period 1995-2014 (Figure 2-1). The increase was mainly accounted for by penicillins, and approximately 87 % of the penicillin products sold for companion animals in 2014 was as a combination of amoxicillin and clavulanic acid.

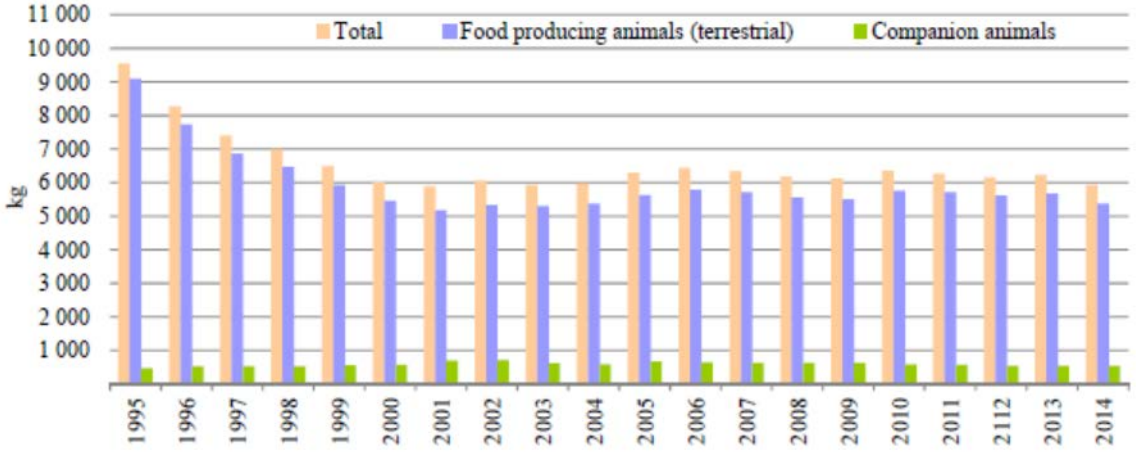

Figure 2-1. Total sales, in kilograms active substance, and estimated sales for food-producing (terrestrial) animals and companion animals of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in Norway for the years 1995-2014. (NORM/NORMVET 2014)

The register of prescriptions available to NFSA, issued by veterinarians and dispensed by pharmacies, was established earlier but not all pharmacies participated in the register before 2015. Therefore it is currently impossible to extract reliable data on antimicrobial consumption in the Norwegian pet population. The number of prescriptions issued for antimicrobials for dogs and cats in Norway during the first half of 2015 is illustrated in Figure 2-2.

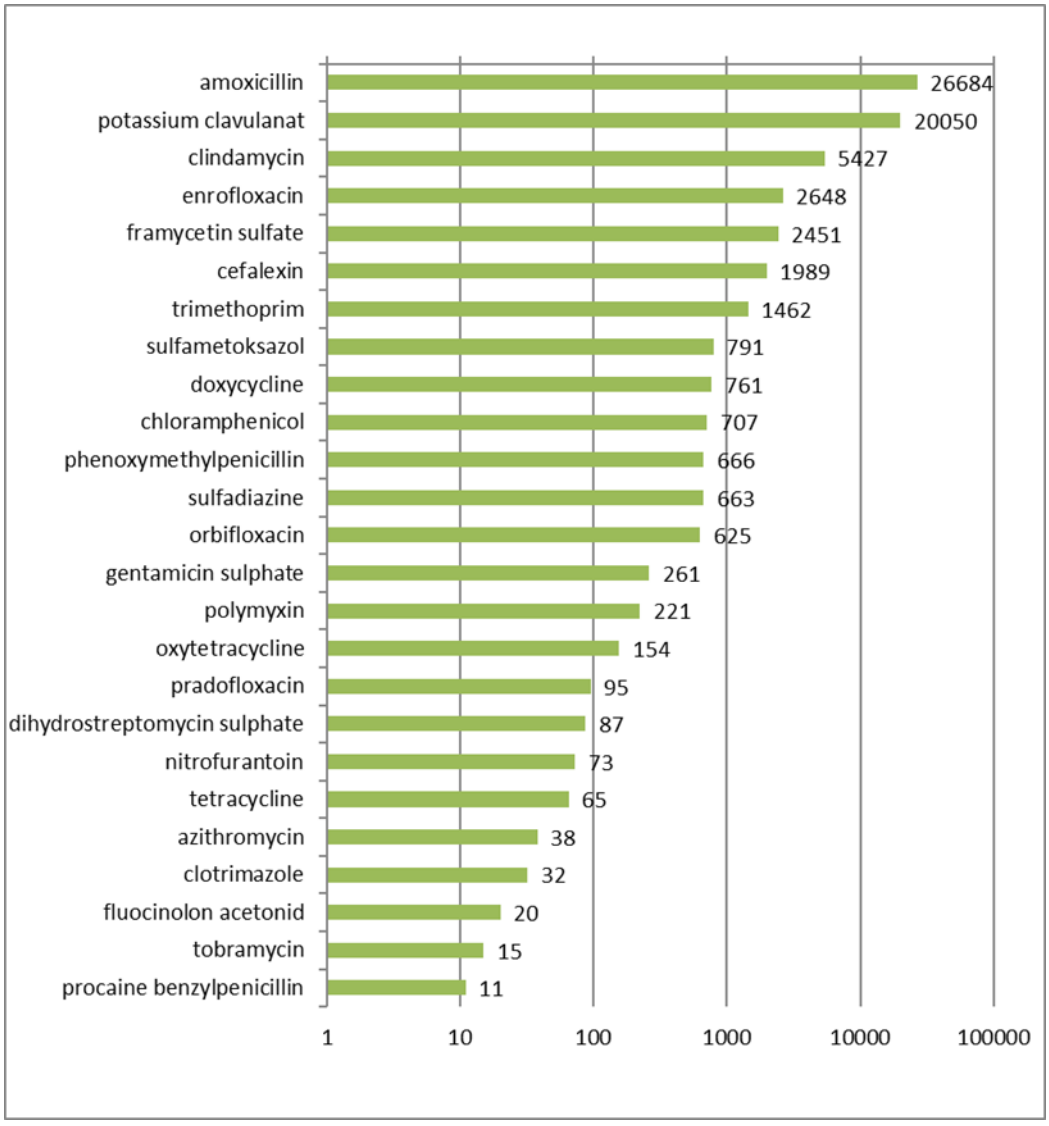

Figure 2-2. Number of prescriptions issued by veterinarians for dogs and cats, Jan-Jun 2015 (383393 prescriptions in total, 65996 antimicrobial prescriptions, not all pharmacies participated in the register from the start)

3 Hazard identification

The hazard identification of this Opinion is implicit in the title and in the ToR.

AMR is considered a **direct hazard** when the bacteria involved in an infection are resistant to antimicrobials. An **indirect hazard** arises through the transfer of bacteria or resistance genes to another bacterium, such as commensal or pathogenic bacteria.

4 Hazard characterisation

4.1 Antimicrobials: modes of action and resistance

4.1.1 Modes of action

Different antimicrobial agents may have different modes of action, as illustrated in Figure 4-1. Antimicrobials may have activity against bacteria by one or several of the following pathways:

1. Inhibition of cell wall synthesis.
2. Inhibition of cell membrane function.
3. Inhibition of protein synthesis.
4. Inhibition of nucleic acid synthesis.
5. Inhibition of other metabolic processes.

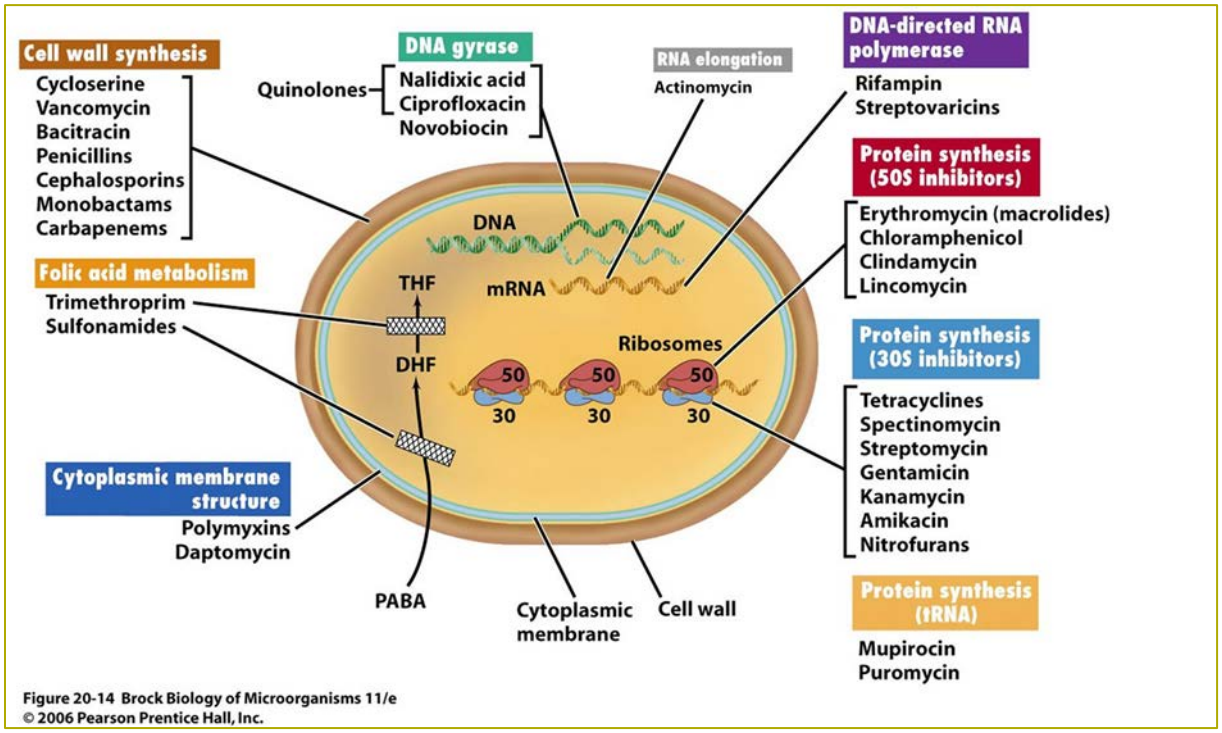

Figure 4-1. The targets of commonly used antimicrobial agents. PABA: Para-aminobenzoic acid; DHF: Dihydrofolate ; THF; Tetrahydrofolate (Madigan and Martinko, 2006)

4.1.2 Antimicrobial resistance

Bacterial infections are described as being clinically resistant if the infection shows a poor response to the drug, even when the maximum dose of antimicrobial agent is administered (Eucast, 2000). Bacteria can acquire resistance to antimicrobial agents through one or several pathways, as listed below and illustrated in Figure 4-2.

- Enzymatic degradation of antimicrobials.
- Modification of the target antimicrobial.
- Alteration in the permeability of the bacterial cell wall.
- Alternative pathways.

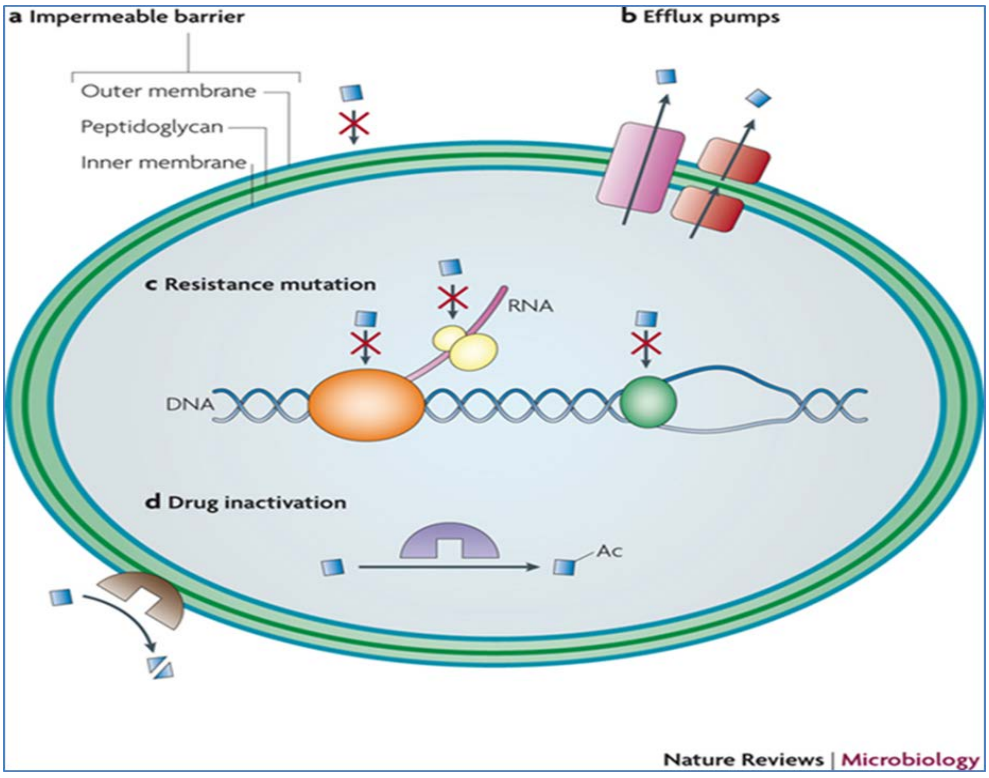

Figure 4-2 Different bacterial resistance mechanisms. Ac: Acetyl group (Allen et al., 2010)

Resistance to antimicrobial agents may be **intrinsic** or **acquired**. Intrinsic resistance is a natural property of an organism, resulting in decreased susceptibility to a particular antimicrobial. Acquired resistance is a result of genetic changes in a microorganism due to mutation or the acquisition of extra-chromosomal genetic material. Although mutations may cause AMR in some cases, the most important mechanism for the acquisition of AMR is horizontal gene transfer (HGT). HGT may occur within species or inter-species by conjugation, transformation, or transduction; this has been extensively described in the review article of Huddelston (2014) and is illustrated in Figure 4-3.

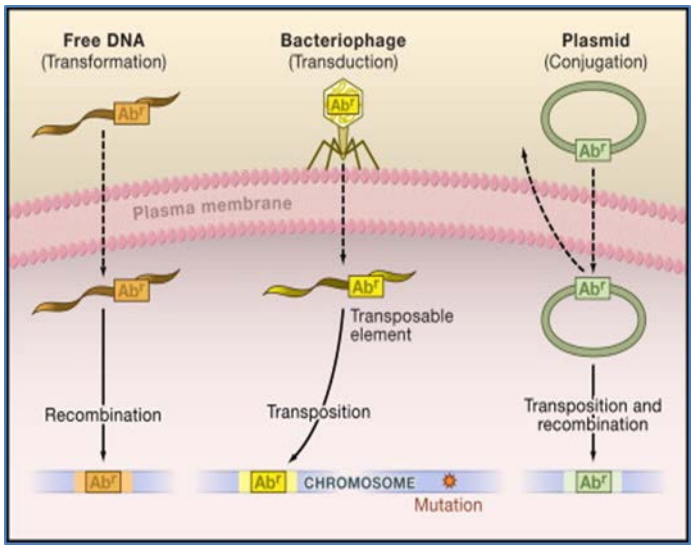

Figure 4-3. Different mechanisms involved in HGT (Foxman, 2012).

For further reading see VKM assessment of AMR in the Norwegian food-chain (VKM, 2015).

4.2 Drivers for Antimicrobial Resistance

All uses of antimicrobials in human and veterinary medicine are possible drivers for the development of AMR in bacteria.

The spread of AMR does not necessarily respect phylogenetic or ecological borders. The resistance to a certain antimicrobial agent can be induced, even by the use of other agents such as antimicrobials, sanitizers and some metal-containing compounds. For example, the human and animal gastrointestinal tracts are reservoirs to enormous species diversity and density, as well as reservoirs for hundreds to thousands of known AMR genes with the mechanisms in place for horizontal transfer of any gene (Huddleston, 2014). The mobility of these AMR genes is attributed to their residence on mobile genetic elements – plasmids, transposons, and integrons (IFT, 2006).

4.3 Pets as a source of bacteria with antimicrobial resistance

AMR genes occur naturally and pre-date the use of antimicrobials in human and veterinary medicine (Aminov and Mackie, 2007; Marshall et al., 2009). However, the number of resistant bacteria, the geographic locations affected by AMR, and the spectrum of resistance in individual bacterial species are increasing. Currently, the prudent use of antimicrobials in human and veterinary medicine is a prerequisite for successful treatment of serious infectious diseases, and is thus a matter of animal welfare (Ewers et al., 2012).

Use of antimicrobials is considered the major reason for the increase in AMR. However, embracing *One Health* approaches, additional factors, concerning environmental, animal, and human health that may contribute to this development, are being studied (Harrison et al.,

2014). One factor involved is the transmission of bacteria with AMR characteristics between animals, between humans, and between animals and humans and the environment, and the spread of resistance genes between animal, human, and environmental strains of bacteria. As microbes live in changing environments, genetic alteration is of utmost importance for bacterial survival (Depardieu et al., 2007). Microbial ecosystems are not isolated and there is extensive gene exchange between different ecological and taxonomic microbial groups (Aminov and Mackie, 2007; Levy, 2002; Salyers et al., 2004). Salyers (1995) states that "almost any bacteria can exchange genes with almost any other bacteria, and probably will, if given a chance". AMR traits can be transferred between resident microbes, microbes in transit, and from harmless to potentially pathogenic bacteria (Levy, 1992; Marshall et al., 2009; Salyers et al., 2004).

Antimicrobial usage is monitored and controlled more closely in food-producing animals than in pet animals. Consumer safety has not been a major issue in the treatment of pets, and medicines, in general, are often prescribed more liberally for these animals. The consequences of treatment failure or disappointing owners who expect treatment, even when a diagnosis is not possible, is often in greater focus than the possible risks associated with overuse of antimicrobials (Guardabassi et al., 2008). This is one consequence of focus being on the health of an individual animal (as occurs in human medicine), whereas population-based approaches are more common in food-producing animals.

Most of the early investigations on transmission of resistant bacteria from animals to humans focused on foodborne pathogens (van den Bogaard and Stobberingh, 2000). However, during the last decades transmission between pet animals and humans has received increasing attention. The impact of such transmission is likely to be enhanced because virtually the same classes of antimicrobial agents are used in human medicine and small animal medicine (Guardabassi et al., 2004b). Examples of common multi-resistant bacteria that currently are a cause for concern are: MRSA, MRSP, extended-spectrum beta-lactamase (ESBL/AmpC) producing enterobacteria (e.g. *E. coli*, *Klebsiella pneumoniae*), and VRE.

However, implying that pet animals may be a major source of human infections neglects the complexity of the scenario (Ewers et al., 2012). Shared environments and shared microbial populations play important roles in the spread of AMR, serving as reservoirs of AMR genes (Gonzalez-Zorn and Escudero, 2012; Harrison et al., 2014). The spread of bacteria between species, between countries, and across continents is increasingly observed, adding to the potential for bacterial transmission between pets and humans. Although traditional molecular typing methods have provided important insights, the direction of transmission needs further investigation. New technologies, such as whole-genome sequencing, allow for more sensitive approaches to understanding the evolution or migration of particular microbial strains (Harris et al., 2013; Harris et al., 2012; Harrison et al., 2013).

Genetic similarities have been observed between multi-resistant isolates from humans and from household pets (Ewers et al., 2012; Loeffler and Lloyd, 2010; Vincze et al., 2013). This implicates interspecies transmission, further supported by more recent studies indicating

contact with pets as a risk factor for human infections with resistant bacteria, and by several case reports suggesting household transmission of resistant strains between pets and their owners (Damborg et al., 2015).

Recently, various multi-resistant bacteria, such as ESBL/AmpC-producing *E. coli*, MRSA, and MRSP, have spread among dogs and cats worldwide (Ewers et al., 2012; Guardabassi et al., 2004b; Wieler et al., 2011). AMR has also been identified in other microbes encountered in small animal practice, including typical human nosocomial pathogens such as carbapenemase-producing *E. coli* and multi-resistant *K. pneumoniae* and *Acinetobacter baumannii* (Muller et al., 2014; Woodford et al., 2014). All these bacteria can be hospital-acquired, and are resistant to virtually all conventional antimicrobials that are licensed for animal use. Hospitalization and antimicrobial treatment, especially with broad-spectrum drugs such as cephalosporins and fluoroquinolones, are major risk factors associated with carriage and infection with multi-resistant bacteria in animals (Weese and van Duijkeren, 2010). Even exposure to penicillin, which is considered a narrow-spectrum antimicrobial, has been shown to promote increased prevalence of resistance to several unrelated antimicrobials among faecal indicator bacteria intrinsically resistant to penicillin (Gronvold et al., 2010a; Gronvold et al., 2010b; Gronvold et al., 2011).

4.3.1 *Staphylococcus* spp.

Staphylococcus aureus is part of the natural microbiota of humans and animals, but has the potential to cause a broad spectrum of diseases. The emergence and spread of MRSA in both hospital and community settings pose a major threat to global health. Since the first description in 1961, MRSA has spread globally with a small number of clones including hospital-acquired (HA)-MRSA (clonal complex (CC) 5, CC22 and CC45), community-associated (CA)-MRSA (CC8, CC30 and CC80), and livestock-associated (LA)-MRSA (CC398) clonal lineages (Ballhausen et al., 2014; Jevons, 1961; Otto, 2012). More recently a number of “multi-host” MRSA lineages have been identified that are capable of colonizing and infecting a broad range of mammalian and avian species (Garcia-Alvarez et al., 2011; Paterson et al., 2012; Walther et al., 2012).

MRSA lineages isolated from companion animals generally match the dominant lineages found in the human populations in the same geographical area (Coelho et al., 2011; Loeffler et al., 2010; Vincze et al., 2013). Transmission of MRSA between humans and pets is described in the literature (Boost et al., 2008; Loeffler et al., 2005; Rutland et al., 2009; van Duijkeren et al., 2004; van Duijkeren et al., 2005; Weese et al., 2006). In most studies the direction of transmission is unclear. Pets may act as a reservoir for human MRSA infection and vice versa, as transmission occurs in both directions (Loeffler and Lloyd, 2010). Harrison et al (2014) demonstrated that a shared pool of HA-MRSA (CC22) isolates could infect both humans and pet animals without undergoing host adaption and the evolutionary origin of the pet animal isolates was likely to be human.

Bidirectional transmission is also described for LA-MRSA (CC398); the original infections were probably human (Lowder et al., 2009), then livestock, and then back to humans (Armand-Lefevre et al., 2005; Price et al., 2012). Furthermore, CC398 was recently isolated from dogs, cats, and horses (Vincze et al., 2014).

In a recent study by Fritz et al (2014) on environmental, pet, and human CA-MRSA strains within households, one of three humans with an infecting or colonizing MRSA strain and a colonized pet carried a strain type that was concordant with their pet's strain. Household environmental surfaces may serve as vehicles for the acquisition and spread of MRSA among household members, including pets (Fritz et al., 2014). Several reports document the spread of CA-MRSA within households and the potential for these strains to cause recurrent infections among family members (Jones et al., 2006). Close contact between household members increases the risk of transmission, and young children appear to be particularly important as reservoirs and potential vectors for CA-MRSA (Knox et al., 2012; Nerby et al., 2011). While most studies focus on dogs, Scott et al (2008) demonstrated that cats were significantly associated with MRSA-contamination of the household environment.

MRSA colonization or infection is a recognized occupational risk for veterinary staff, and some studies have identified the same MRSA strains in people and pets sharing the same household (Weese and van Duijkeren, 2010). Although the most common MRSA clones infecting or colonizing pets (e.g. ST22) occurred in humans long before their emergence in pets, and are likely to originate from humans, pets may serve as reservoirs for MRSA infection or (re)colonization of humans (Loeffler and Lloyd, 2010).

Methicillin-resistant *S. pseudintermedius* (MRSP) is increasingly reported in pet animals worldwide and cases of human infections have been described (Campanile et al., 2007; Kempker et al., 2009; Stegmann et al., 2010). Transmission between dogs and humans has been documented (Morris et al., 2010; Sasaki et al., 2007; van Duijkeren et al., 2008). *S. pseudintermedius* is a commensal and opportunistic pathogen in pet animals, and its occurrence in humans is mainly limited to small animal veterinarians and pet owners (Bannoehr and Guardabassi, 2012)). In a study by Paul et al. (2011), MRSP strains corresponding to emerging clones in the European pet population were isolated from Italian veterinarians, with a carriage rate of 3.9 % (n=128). Considering that *S. pseudintermedius* has a canine origin and is not a commensal in people, the relatively high MRSP carriage rates (up to 8 %) among owners of infected dogs and veterinarians provide indirect evidence of transmission (Ishihara et al., 2010; Walther et al., 2012). MRSP infections have been reported in dog owners and their frequency may be underestimated due to diagnostic problems regarding identification of *S. pseudintermedius*, and consequently MRSP, in human clinical microbiology laboratories (Pottumarthy et al., 2004).

A review by Moodley et al (2014) on MRSP and methicillin-susceptible *S. pseudintermedius* (MSSP) highlighted the inconsistency between published studies regarding antimicrobial susceptibility testing methods and interpretation criteria, and encouraged systematic surveillance at a national or EU level.

Chanchaithong et al (2014) investigated methicillin-resistant coagulase-positive staphylococci (MRCoPS) in dogs, in humans associated with dogs, and in humans not associated with dogs. The same MRCoPS strains were isolated from dogs, dog owners, and veterinarians, indicating interspecies transmission. However, MRCoPS was not isolated from humans not associated with dogs.

Methicillin-resistant staphylococci have also been isolated from healthy pet animals, indicating a potential reservoir for multi-resistant staphylococci (Chan et al., 2014; Davis et al., 2014; Kjellman et al., 2015; Schmidt et al., 2014).

Data on occurrence of resistance in coagulase-negative staphylococci in pets are sparse. One study highlights the emergence of cases of otitis externa due to coagulase-negative staphylococci and emphasizes the need for bacterial culture, with species identification and susceptibility testing of swab specimens from the ear canal in order to ensure that appropriate antimicrobial agents are prescribed (Lilenbaum et al., 2000).

4.3.2 *Enterococcus* spp.

Ampicillin resistance is a marker for hospital-associated *Enterococcus faecium*. Healthy dogs have been shown to be frequent carriers of ampicillin-resistant *E. faecium* (Damborg et al., 2009). However, the virulence gene profiles of the canine strains in this study apparently differed from the human strains. Vancomycin-resistant enterococci (VRE) harbouring VanA or VanB were not detected in a study on the prevalence in dogs and cats subjected to antimicrobial pressure (Kataoka et al., 2013), but possible links between human and canine VRE isolates have previously been described (Manson et al., 2003; Willems et al., 2000).

4.3.3 ESBL/AmpC

A study by Hordijk et al (2013) showed that the prevalences of extended-spectrum β-lactamase-producing and AmpC-producing *Enterobacteriaceae* (ESBL/AmpC) in cats and dogs were relatively high, and there were genetic similarities with those found in isolates of both humans and food-producing animals. Despite numerous studies on ESBL/AmpC-producing bacteria from different sources, routes of transmission are still to be unravelled. Exposure to pet animals has been identified as a risk factor for carriage of ESBL/AmpC-producing bacteria in humans in two separate studies (Leistner et al., 2013; Meyer et al., 2012). Other evidence supporting a role for household pets in human ESBL/AmpC infections include the occurrence of specific ESBL/AmpC-producing *E. coli* clones (e.g. B2-O25b:H4-ST131 and CTX-M-15-ST648) and ESBL/AmpC types (e.g. CTX-M-15 and CTX-M-1) in both people and pets (Ewers et al., 2012). The epidemiology of ESBL/AmpC-producing *E. coli* present in humans and pet animals indicates that human-to-human transmission is the most important route of distribution of AMR (Ewers et al., 2012). Whether human strains were the source of the recent enrichment of ESBL/AmpC-producing *E. coli* in animals is unknown, although some publications suggest this as a possibility (Ewers et al., 2012; Wu et al., 2013).

Bortolaia et al. (2014) compared plasmids encoding CMY-2 β-lactamase among clinical *E. coli* isolates from humans and pet animals in the same region. The results revealed a heterogeneity of plasmid backgrounds, suggesting limited exchange between the two populations, as the blaCMY-2 occurred at very different frequencies and was harboured by distinct plasmid types.

Osugui et al. (2014) studied extra-intestinal pathogenic *E. coli* (ExPEC) strains isolated from dogs and cats, and found pathotypic and phylogenetic similarities between human isolates and multi-resistant genotypes. A study on pet animals by Ewers et al (2012) described a possible novel ExPEC-genotype combining multi-resistance, virulence, and zoonotic potential.

4.3.4 *Campylobacter* spp.

A study by Tenkate and Stafford (2001) showed that approximately 6 % of human enteric campylobacteriosis is transmitted from pets, and that these animals probably represent potential sources of AMR spread due to their close contact with humans (Guardabassi et al., 2004b). Damborg et al (2004) showed direct evidence of the transmission of fluoroquinolone-resistant *Campylobacter jejuni* between humans and pets living in the same households. *Campylobacter* spp. may cause diarrhoea in dogs, and having a dog in the household has been identified as a risk factor for human campylobacteriosis in Norway (MacDonald et al., 2015).

In contrast, a comparative study by Damborg et al (2008) on human and canine *C. upsaliensis* isolates indicated that dogs are not the main source of human infection as the majority of the human strains clustered separately from the canine strains.

4.4 Surveillance of antimicrobial resistance in bacteria from animals in Norway; NORM-VET

The NORM-VET monitoring programme for AMR in the veterinary and food-production sectors was established in year 2000 and is coordinated by the Norwegian Zoonosis Centre at the Norwegian Veterinary Institute. The results have been published every year in a joint report, together with the results from NORM. The programme monitors AMR among zoonotic bacteria, such as *Salmonella* spp. and *Campylobacter* spp. (based upon EU Directives), indicator bacteria, and clinical isolates from submissions to the Norwegian Veterinary Institute. Monitoring of zoonotic bacteria reflects the actual burden of these bacterial species within the animal populations of Norway, whereas sampling clinical isolates is passive in nature, and depends on the disease situation and the submission of samples to the Norwegian Veterinary Institute by farmers and veterinarians.

The frequencies of reported resistance in bacteria from pet animals are low to moderate, and the situation has been stable since the start of the Norwegian monitoring programme for AMR in the veterinary sector (NORM-VET 2000, 2002, 2004. 2006, 2007, 2008, 2012 and 2013 www.vetinst.no) in year 2000.

The prevalence of AMR among certain bacteria of the normal enteric microbiota can serve as an indicator of the selective antimicrobial pressure in various populations. These bacteria may form a reservoir of transferable resistance genes from which AMR can spread to other bacteria, including those responsible for infections in animals or humans. Thus, monitoring resistance among indicator bacteria of the normal enteric microbiota from healthy animals, as well as from feed and food, is important for obtaining an overview of the resistance situation, detecting trends, and evaluating the effects of interventions. In NORM-VET, *E. coli* and *Enterococcus* spp. are used as indicator bacteria.

Monitoring among the EU member states (including EEA-member states) has been harmonised by EFSA from 2014 and onwards. This means that a more comparable reporting system on the occurrence of AMR in bacteria from animals and products of animal origin will be available in the future.

Substances included in the test panels and some of the epidemiological cut-off values applied in NORM-VET have been changed over the years, making it difficult to compare data and search for trends. Only substances that were monitored in 2013 are presented in the Table 13-2. Other substances belonging to the same antimicrobial class and that have been previously monitored and could be compared are included where appropriate.

5 Exposure

If AMR bacteria are shed, then bacteria in urine or faeces are of interest. For direct contact between dogs, and between dogs and humans, skin-skin and mouth-skin contact are relevant and AMR in skin, oral, and throat bacteria is of interest.

A vast, and largely unexplored, reservoir of resistance genes is likely to be present in non-pathogenic bacteria in the environment or existing as commensal agents. Studies using metagenomics have highlighted the unappreciated diversity of AMR genes in the human microbiome, and genes that had not been described previously were identified (Penders et al., 2013). Thus, the potential reservoir for resistant microbes and/or resistance genes in the human, animal, and environmental microbiomes remains to be explored. Interspecies microbial transmission is complex, and its implication is inadequately understood.

5.1 Exposure routes

5.1.1 Antibiotic treatment of pets

The prevalence of bacteria with antimicrobial resistance characteristics in the pet population varies considerably between countries. The reason for this geographical variation is unclear, but probably relates to local variations in patterns of antimicrobial use. Any use of antimicrobials exposes bacterial pathogens and the resident microbiota to varying concentrations of antimicrobial drugs for variable times. This creates selection pressures that

can result in emergence of resistance and/or an increase in the abundance of resistant bacteria. Antimicrobial use can result in AMR in the species being treated, and resistant microbes or resistance traits can be transmitted bi-directionally between animals and humans.

We have limited information on veterinary practices, but developments in veterinary science often lead to more animals being treated, and more animals being treated over longer periods with antimicrobials. This is especially relevant for chronic skin diseases, where prolonged treatment is often indicated. Treatment patterns in pets is today are very similar to those in humans.

5.1.1.1 Direct and indirect routes of transmission

The relationship between many pet animals and their owners has changed during recent decades (Franklin, 1999). Today, many pet animals commonly live as family members in the household, in close contact with their owners. Consequently, the possibilities for transmission of microbes and genes have increased. Transmission potentially occurs in both directions (Figure 5-1), and possible zoonotic spread of resistant bacteria is thus well documented (Ewers et al., 2012). Interspecies transmission between pets and humans, and between pets and other animal species, can occur by direct contact or indirectly through environmental contamination of households, veterinary clinics, and public spaces.

The exposure routes of importance for transmission of AMR are very complex. Whereas the importance of antimicrobial treatment for developing direct AMR in humans and animals are clear, tracing the chains of interactions between pets and humans is complicated because pets and owners share a common environment, and are all indirectly linked to pets/humans through the environment.

Cats and dogs represent different physical interactions within their own species and between their own species and humans, but share the common feature of physically close contact with their owners/ family. While several reports document this, the magnitude of the interactions is not well documented. Contact between a pet and its owner is more intense than the contact between humans and pets that they do not themselves own, but these pets may still be important in the spread of bacteria or AMR to new clusters of pets/ families.

Humans in close contact with dogs or cats are further exposed to the microflora acquired by the pet in parks, streets, leftover foods, etc. and will share a considerable part of the microbial flora, including resistant bacteria and resistance genes. While the pet/owner/family is the major arena for interaction, pet populations are meta-populations, and their behaviour and way of life represent a common environment in which they shed and consume bacteria.

In urban areas with many pets, AMR is likely to be found in bacteria in the environment, even if they are shed by only a low proportion of pets. Most pets that are allowed outdoor access will both be exposed to, and shed, bacteria and bacterial genes by defecating, urinating, eating, licking, and salivation. Dogs are scavengers and may therefore be more

likely to bring problematic microorganisms into the family than cats. Cats are more solitary animals, but the cat litter box may nevertheless represent an area of contact.

5.1.2 Food

Pets are fed everything from food scraps to food that is primarily intended for humans, dried food, canned food, and raw food from slaughtered animals. We assume that food produced by families as leftovers from meals do not represent a significant problem, and focus on feed from external, commercial sources. The pet feed market is dominated by a wide variety of dried, pelleted feed. While these products may contain intact AMR genes, they are unlikely to be of major importance in transmission of AMR compared with the use of raw meat from slaughtered animals.

In year 2000, a total of 70 *E. coli* isolates from dog feed (meat by-products) were included in the NORM-VET programme. Of these, 19 isolates were resistant to one or more different antimicrobials. Resistance to streptomycin, tetracycline, sulphonamides, and ampicillin was most common. One isolate was resistant to the cephalosporin cefuroxime, but no reduction in susceptibility towards the quinolones nalidixic acid or enrofloxacin was observed.

In recent years, an increasing number of pet owners have become interested in feeding raw food, particularly for pet dogs, rather than commercial dry food. Raw feed is typically bought frozen, but some owners prefer it to be fresh. The volume of frozen feed can be illustrated by a major Norwegian producer (http://www.vomoghundemat.no/) that has increased production of their product and now sells approximately 4000 tonnes/year of raw feed produced from meat and offal from chicken, sheep, cattle, and pigs. In addition, raw pet feed can be imported from the EU provided that a *Salmonella* certificate is presented and specific criteria for the level of *Enterobacteriaceae* (<5000/g) can be documented. Detailed regulations for this import are linked to regulations for import of animal by-products (Mattilsynet, 2015). No associations have been detected between the prevalence of *Campylobacter* spp., *Clostridium difficile*, MRSA, or VRE carriage and canine consumption of raw meat (Lefebvre et al., 2008; Olkkola et al., 2015). However, two studies in Canada found an association between raw meat consumption and shedding of specific *Salmonella* serovars and extended-spectrum cephalosporinase *E. coli* (Lefebvre et al., 2008; Leonard et al., 2011). Outbreaks of infection in humans have been linked to imported chewing bones in Norway, but the level of *Salmonella* has been reported to be very low (Pettersen and Bernhoft, 2014). Using meat/offal from chicken should be expected to bring *Campylobacter* into the family, but as *Campylobacter* is not freeze-tolerant should not be a problem with frozen feed. The increasing occurrence of AMR in food-producing animals in Europe and, to a certain extent, in Norway means that raw food provided as feed for Norwegian dogs represents contact between dogs and the pool of AMR in bacteria from domestic animals, and, to a certain extent, also in the international population of domestic animals. Such imports may be of major significance in assessing the probability for spreading AMR within Norway.

An interesting aspect of dogs is their evolutionary capacities as scavengers to avoid infections through eating sick and dead animals for millennia. Could this explain the so far limited documentation of transfer through dogs to humans?

5.1.3 An open population

Up to 10 years ago, the Norwegian populations of dogs and cats could be considered as closed populations. In contrast, today's travel with animals and relatively unregulated import, especially of dogs, represents an open population. We have little information about the infectious status of imported dogs, but some studies indicate major differences from the Norwegian domestic population (Hamnes et al., 2013; Høgåsen et al., 2012; Klevar et al., 2015). Furthermore, many dogs also travel, mainly inside the EU/EEA, due to the relaxation of regulations. In Norway, import of dogs is allowed provided that the regulations are followed – these are largely linked to rabies vaccination certificates and treatment of *Echinococcus multilocularis* infection.

Travel to areas in which there are high endemic levels of bacteria that are resistant to antimicrobials has been indicated as a risk factor for the acquisition of such bacteria (van der Bij and Pitout, 2012). Several studies have shown that international travel is a major risk factor for colonization with ESBL/AmpC-producing *Enterobacteriaceae* spp. (Kennedy and Collignon, 2010; Ostholm-Balkhed et al., 2013; Paltansing et al., 2013; von Wintersdorff et al., 2014). These resistant strains are probably acquired from the environment during travel (Collignon et al., 2009). Most studies have been conducted on human travellers, but there is no reason to believe that microbiota in pets will behave differently. The microbiome of both humans and pets interact with microbes from travel-related environments and populations, and the effect of international travel on AMR is unlikely to be limited to known pathogens or opportunistic pathogens.

In summary, Norwegian dog populations are in contact with the whole European dog population, with the long-term implication that the Norwegian human population will also be exposed to AMR patterns introduced to Norway by travelling dogs and dogs imported from other countries. While information for dogs is limited, data on cats are even scarcer. Cats are mainly imported for breeding purposes, and travel with cats occurs less frequently than with dogs.

5.2 Modelling exposure and interaction

Risk assessment models are not easily established in this area, and a paper by (Berendonk et al., 2015) illustrates the complexity of this task and the information required to develop accurate risk assessment models for AMR.

Theoretical models represent a necessary element of risk assessments, as well as a bridge towards understanding the link between empirical data and the context of the actual situation. Figure 14-1 (Appendix II – Exposure models) represent similar approaches to

understanding the complexity of the situation. Notably, Figure 5-1places domestic pets in a subordinate position to food-producing animals. Some papers discuss this, and the following statement (Barber et al., 2003a) seems to be relevant "*We suggest that the role of food-producing animals in the origin and transmission of antimicrobial resistance and "foodborne" pathogens has been over-estimated and over-emphasized in the scientific literature; consequently, non-foodborne transmission, including pet-associated human cases, has been under-emphasized*".

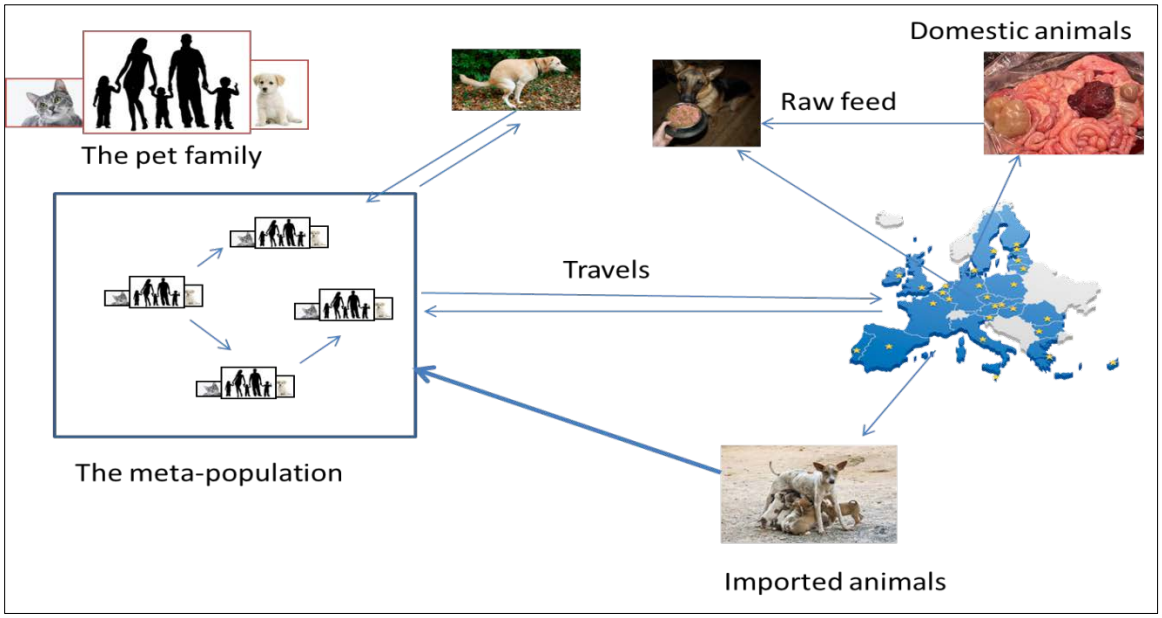

Figure 5-1. Diagram showing the possible position of domestic pets in the transfer of AMR to bacteria infecting humans.

A major challenge in theoretical models is differentiating between the observed short-term effects of this transfer and the more long-term effects created by emerging patterns of AMR. Thus, one plausible description of the current situation could be that the use of antimicrobials in dogs is of marginal importance in the short-term, but may dominate through environmental contamination over time.

5.3 Summary of Chapter 5

Within Norway and the rest of Europe, pets represent open populations. In practice, pet populations are in contact with pets in other countries, especially inside the EEA, through regular and irregular import of animals and also through contact with the European pool of domestic animals through imported raw slaughter material.

Regardless of the theoretical model used to describe exposure routes and their importance, empirical data are needed to put into the models as the values of the parameters defining the behaviour of the model. Not only is there a major lack of information about AMR patterns in the Norwegian pet populations, but there is also a lack of information about the

importance of transboundary movements of pets, and on AMR patterns found in bacteria from imported pets.

6 Probability characterisation

Risk characterization is defined as the qualitative and/or quantitative estimation, including attendant uncertainties, of the probabilities of the occurrence and the severity of known or potential adverse health effects in a given population, based on hazard identification, hazard characterization, and exposure assessment. In this assessment, the focus is on the probability of transfer as the data are insufficient to assess the risk of transmission of resistant bacteria or antimicrobial resistance determinants between household pets and humans.

Significant public health concerns exist because of the probability of animal-to-human transmission of resistant clones and/or resistance genes. Several studies document that bi-directional transmission occurs. Most studies relate to specific pathogens or susceptibility testing of indicator bacteria, and the choice of indicator bacteria has largely been based on clinical relevance and cultivability of these organisms.

The most common methicillin-resistant *S. aureus* (MRSA) clones isolated from pets occurred in humans long before their emergence in pets, and are likely to originate from humans. However, pets may serve as reservoirs for MRSA infection or (re)colonization of humans (Loeffler and Lloyd 2010). *S. pseudintermedius* is a commensal and opportunistic pathogen in pet animals and its occurrence in humans is mainly limited to small animal veterinarians and pet owners (Bannoehr and Guardabassi, 2012).

Several isolates of extended-spectrum β-lactamase-producing and AmpC-producing *Enterobacteriaceae* (ESBL/AmpC) from different human and animal sources are genetically similar, but routes of transmission are still to be ascertained.

In most studies on human and canine *Enterococcus* spp. and *Campylobacter* spp., the majority of the human strains cluster separately from canine strains. However, possible links between human and canine isolates have also been described (MacDonald et al., 2015).

6.1 Factors that contribute to interspecies transmission of antimicrobial resistance

6.1.1 Use of antimicrobial agents

According to NORM/NORM VET, an increase in sales of antimicrobials marketed for companion animals of 19 % was observed in Norway between 1995 and 2014. The increase was mainly accounted for by penicillins, and approximately 87 % of the penicillin products sold for companion animals in 2014 was as a combination of amoxicillin and clavulanic acid.

Since 2005, annual increases in the use of extended-spectrum penicillins and beta-lactamase resistant penicillins have been observed in human medicine in Norway, and penicillins currently account for approximately 40 % of the total antimicrobial use in humans. There has also been a marked increase in quinolone use in human medicine over the past ten years (NORM/NORM-VET, 2015).

The occurrence of multi-resistant bacteria in household pets has resulted in a global increase in veterinary use of critically important antimicrobials (CIAs) that are authorized for human use only (Weese, 2008; Weese et al., 2006). However, sales of antimicrobial drugs defined by the World Health Organization (WHO) as being of highest priority for human medicine, i.e., fluoroquinolones and macrolides, are negligible in veterinary medicine in Norway (NORM/NORM-VET, 2015).

The relative impact of antimicrobial use in humans and in animals on AMR emergence is a complex issue with important data gaps (Weese et al., 2015).

6.1.2 Open population

Interspecies transmission between pets and humans, and between pets and other animal species, can occur by direct contact or indirectly through environmental contamination of households, veterinary clinics, and public spaces.

Environmental and shared microbial populations play important roles in the spread of AMR by serving as reservoirs of AMR genes (Gonzalez-Zorn and Escudero, 2012; Harrison et al., 2014). The spread of microbes between species, between countries, and across continents is increasingly observed. International travel enables interactions between the microbiota of both humans and pets with microbes from travel-related environments and populations. Although the consequences of these changes in the microbial genetic pool are difficult to predict, the introduction of resistance traits may create opportunities for horizontal transfer to other bacteria, and interspecies transmission of resistant microbes.

Little is known about the duration of travel-acquired resistant organisms in the human or pet microbiota, but their continued viability plays a key role in the likelihood of spreading these organisms or resistance traits further.

Travelling represents a potential risk for international transfer of AMR bacteria. Studies that focus on the AMR of the microbiota as a whole are necessary in order to obtain better information on direction and epidemiology of the transfer.

6.1.3 Pet food

As the majority of microbiota are neither pathogenic nor readily cultivated, the possible risks from raw feed-to-animal-to-human transmission of resistant clones and/or resistance genes remains to be explored.

6.2 Qualitative description of probability

The rankings “Negligible,” “Low,” “Medium,” “High” and “Not Assessable” are used for qualitative determination of the probability of human exposure to a given AMR in a given food or feed commodity, animal species, or plant. The different ranking categories are defined below (CAC, 2012):

- Negligible – The probability of exposure for susceptible people is extremely low;
- Low (Unlikely) – The probability of exposure for susceptible people is low but possible;
- Medium (Likely/Probable) – The probability of exposure for susceptible people is likely;
- High (Almost Certain) – The probability of exposure for susceptible people is certain or very high;
- Not assessable – The probability of exposure to susceptible people cannot be assessed.

In this assessment all ranking categories other than “**negligible**” have been combined into a single category “**non-negligible**” (see later).

In Norway, the probability for transfer of AMR associated with pet animals can be summarized as shown in Table 6-1. Based on available data regarding occurrence of AMR in pet animals, the probabilities may be classified as either negligible or non-negligible. In this assessment these categories have been defined as follows:

Negligible – the probability of exposure for transfer of AMR is extremely low. A negligible probability should be considered insignificant.

Non-negligible – the probability of exposure for transfer of AMR is greater than negligible. The non-negligible probability should be considered significant, but the data are currently insufficient to enable distinctions to be made between the different levels or to determine whether one probability is greater or less than another in the same category.

The following factors have been identified as being relevant for increasing the development and dissemination of AMR to such an extent that the probability of direct or indirect transfer of AMR between pets and humans in Norway should be regarded as non-negligible:

- Use of antimicrobials. This use is considered to be the major reason for the increasing resistance trends, and a general driver for development and spread of AMR.
- Therapeutic use of antimicrobials in the dog and cat populations. This is particularly important with regard to therapeutic treatments that promote the development of MRSA, MRSP, and ESBL/AmpC-producing *Enterobacteriaceae*.

- The Norwegian dog population being part of an open population with extensive international contacts. The VKM Panel and Work Group have assumed that the Norwegian cat population is less exposed to an open, international population than the Norwegian dog population. However, documentation to verify this assumption is lacking.
- Use of raw pet food of animal origin in Norway. This use has been identified as an important exposure route for AMR that may increase the level of AMR in bacteria in pet animals. Scientific documentation for the classification of this probability is lacking.

6.3 Summary of probability characterisation

Table 6-1. Factors associated with development of AMR and affecting the probability of AMR transmission between bacteria in pets and humans. The classification is based on VKM's expert opinion

	Probability for transmission is Negligible		**Probability for transmission is Non-negligible**		**Comment**
	Documented	Insufficient documentation	Documented	Insufficient documentation	
Total use of antimicrobials (animals and humans)			x		General driver for development of resistance pool in the society and environment
Dogs					
Therapeutic use of antimicrobials			x		
Open population			x		Considerable driver for dissemination of AMR
Pet food				x	Includes raw and insufficiently processed food or treats of animal origin
Cats					
Therapeutic use of antimicrobials			x		
Open population		x			
Pet food		x			

7 Uncertainties

The degree of confidence in the final estimation of probability depends on the variability, uncertainty, and assumptions identified in all previous steps. Differentiation of uncertainty and variability is important in subsequent selection of risk management options.

Biological variation includes the differences in virulence that exist in microbiological populations and variability in susceptibility within the human population and particular sub-populations. (http://www.fao.org/docrep/005/y1579e/y1579e05.htm). According to EFSA's guidance regarding uncertainties (EFSA, 2007), assessments should state clearly and unambiguously which uncertainties have been identified and their impact on the overall assessment outcome.

The risks attributable to transmission of AMR microbes or resistance determinants between household pets and humans are difficult to quantify due to a multitude of knowledge gaps, mainly because most knowledge on microbes transmissible by household pets relies on case reports.

In this assessment, a number of uncertainties related to the probability of transmission of AMR from pets to humans have been identified. Many of these uncertainties overlap with the Data gaps.

Bacteria are living organisms under continuous evolution, and are able to adapt rapidly to changing living conditions. This report assesses the current situation regarding development and dissemination of resistant bacteria and their resistance genes between pets and humans. This situation may change as the bacteria continue to adapt to the selection pressures exerted by the worldwide use of antimicrobials. Such changes, sometimes occurring in "quantum leaps" due to HGT, may also rapidly change the probability of transfer of resistance to specific antimicrobials. An example of such an evolutionary event is the recent discovery of plasmids encoding resistance towards colistin (Liu et al., 2015). There is therefore considerable uncertainty associated with the probability characterizations due to future bacterial evolution.

8 Exposure-reduction measures

Antimicrobial treatment is a well-known risk factor for development of AMR. Rational and optimal use of antimicrobials, including susceptibility testing prior to treatment, has the potential to prevent further development of AMR bacteria, both in household pets and humans, and to reduce the probability of interspecies transmission.

Current treatment patterns for pets are very similar to those for humans, and the same criteria (culturing and susceptibility testing) used before treatment can reduce the development of resistance. Minimal veterinary use of CIA that are licensed only for use in humans can reduce the development of the resistance to those antimicrobials. Use of broad-spectrum antimicrobials licensed for veterinary use (e.g. cephalosporins and fluoroquinolones) should be controlled by implementation of antimicrobial stewardship programmes at both the national and the clinical level (Guardabassi and Prescott, 2015). Development of new, narrow-spectrum, veterinary-specific antimicrobial products, including anti-infective biological agents, such as phage and bacteriocins, is urgently needed for treatment of AMR infections in household pets.

Education is a key element in reducing the probability of transmission of AMR associated with household pets. Certain microbial infections that are transmitted by household pets, such as MRSP infections, may be underdiagnosed by physicians. This is partly due to insufficient diagnostic tools, but also reflects the lack of awareness by primary healthcare practitioners about zoonoses transmitted by pet animals, and difficulties in communication between veterinary and medical practitioners. The necessary space and attention should be given to companion animal zoonoses in medical and veterinary university curricula, as well as in continuing education, for example by organizing joint courses and seminars for veterinarians and doctors. Education about the zoonotic risks associated with household pets should be extended to animal caretakers and pet owners, who often do not perceive pets as possible sources of infection, indirectly increasing exposure and infection probability.

9 Conclusions (with answers to the terms of reference)

9.1 Answers to the questions

1. Which bacteria are most likely to transfer AMR between pets and humans (under Norwegian conditions)? Considering both direct and indirect transfer.

According to current knowledge *S. aureus*, *S. pseudintermedius,* and *Enterobacteriaceae* spp. are the bacteria of most concern that may most frequently transfer AMR directly between pets and humans.

However, the literature is limited and there is no evidence to implicate specific bacteria as being most likely to transfer the resistance directly or indirectly between pets and humans. The majority of the resident microbiota have yet to be explored.

a. Which antimicrobials used in the treatment of dogs and cats are most likely to induce resistance?

Broad-spectrum antimicrobials, such as cephalosporins and fluoroquinolones, are traditionally associated with resistance promotion. The extensive use of amoxicillin and clavulanic acid can promote the same type of resistance as cephalosporins. In addition, it is known that even narrow-spectrum antimicrobials, such as phenoxymethylpenicillin, can induce and promote resistance in bacteria.

Therefore, according to current knowledge all antimicrobials used in treatment of pets should be considered as having the potential to induce and promote resistance in microorganisms.

b. Are dogs and cats reservoirs for bacteria that can cause illness and simultaneously transfer resistance? If so, which are these bacteria?

Dogs and cats can be reservoirs of several microorganisms like *S. aureus*, *S. pseudintermedius,* and *Enterobacteriaceae* spp. that are likely to cause illness in humans. They all have the potential to transfer resistance to other bacteria.

2. To what extent are antimicrobial drugs used for pets. This applies both to antimicrobial pharmaceuticals for animals and human drugs. Which drugs are being used, and how much, and for which indications?
   a. Human medicinal products (HMP)
   b. Veterinary medicinal products (VMP)

The register of prescriptions available to NFSA, issued by veterinarians and dispensed by pharmacies, was established earlier but not all pharmacies participated in the register before

2015. Thus, it is presently impossible to extract reliable data on the true consumption of HMP and VMP in pet populations.

3. Which risks exist for direct transmission of resistant bacteria between pets and humans under Norwegian conditions?

and

4. Which risks exist for indirect transfer of resistance genes between pets and humans (under Norwegian conditions) via the respective bacteria?

The following factors have been identified as increasing the development and dissemination of AMR to such an extent that the probability for direct or indirect transfer of AMR between pets and humans should be regarded as non-negligible:

- Use of antimicrobials.
- Therapeutic use of antimicrobials in the dog and cat populations.
- The Norwegian dog population being part of an open population with extensive international contacts.
- Use of raw pet food of animal origin.

5. Which risk reduction measures will be most effective at reducing the increase in resistance?

a. WHO has defined antimicrobials that are critical for human use. Will banning these in the treatment of dogs and cats have any effect on increases in AMR.

Minimal veterinary use of CIAs licensed for humans only may reduce the development of resistance to those antimicrobials.

b. Guidelines for handling pets with (risk) resistant bacteria (as in health care)

Guidelines and education about the zoonotic risks associated with household pets can help to decrease the probability of the transfer of AMR. Awareness of primary healthcare practitioners about zoonoses transmitted by pet animals and efforts to improve communication between veterinary and medical practitioners could facilitate timely diagnosis and identification of resistant strains. Providing the necessary space and attention for companion animal zoonoses in medical and veterinary university curricula, as well as in continuing education, for example by organizing joint courses and seminars for veterinarians and doctors, can raise awareness and identify possible emerging resistant strains.

c. Clarification of the duty of notification upon detection of resistant bacteria

Clear diagnostic routines and reporting lines can lead to clearer pictures being obtained on the existing prevalence of resistance in pet populations, as well as provide information on the possible pathways for spreading of AMR.

6. Which bacteria are good indicators for surveillance of resistance in dogs and cats?

The prevalence of AMR among certain bacteria of the normal enteric microbiota can serve as indicators for the selective antimicrobial pressure in various populations. These bacteria may form a reservoir of transferable resistance genes from which AMR can spread to other bacteria, including those responsible for infections in animals or humans. Thus, monitoring resistance among indicator bacteria of the normal enteric/skin microbiota (*E. coli*, *Enterococcus* spp., and *S. aureus*) from healthy animals, as well as from feed and food, is important for obtaining an overview of the resistance situation, detecting trends, and evaluating the effects of interventions.

10 Data gaps

There is a lack of data regarding the vast reservoir of AMR in the environment, pet animals, and human reservoirs. Furthermore, there is lack of data regarding the routes and frequencies of transmission of AMR from pet animals to humans, and vice versa:

Specific gaps are listed below:

- Data regarding both the levels of carriage of bacteria with AMR in pets and the risk factors associated with the transfer of the bacteria to humans who have contact with infected pets.
- Data about the use of drugs in pets, not only the use registered through official sources and Norwegian veterinarians but also about owners' import of drugs.
- Large-scale, case-control studies to identify human-pet interactions that pose a risk for human disease. Population attributable fractions should be calculated to understand the relative contributions by household pets to microbes that may also be acquired from other sources.
- Baseline data on prevalence and antimicrobial susceptibility on most microbes in the relevant pet populations. Adequate surveillance of pet-associated microbes in large regions like Europe requires a centrally coordinated network collecting data from individual countries. Mandatory reporting for selected microbial agents that are already reportable in humans would help identify common geographical or temporal trends in humans and pets.
- Robust and sensitive diagnostic tests provide the basis for further surveillance and research activities. Research is needed to develop new, rapid, and reliable diagnostic tests, as well as to improve the performance of those currently available. Certification of diagnostic laboratories and definition of minimum quality standards are required to ensure best practices in veterinary diagnostic laboratories, including in-house diagnostic facilities located within veterinary clinics.
- AMRs pattern in Norwegian pet populations and the importance of transboundary movements of Norwegian pets, as well as AMR patterns found in imported pets.

11 Recommendations

Harmonized data collection

We recommend harmonized data collection on susceptibility of important companion animal pathogens to enable more precise comparisons of susceptibility patterns between studies. One way to accomplish this would be through systematic surveillance, either at the country-level or at a larger-scale across countries e.g. EU level.

Studies of AMR in urban areas

In order to be able to measure the possible impact of the spread of AMR between pets and humans, it may be reasonable to focus on urban areas with many imported pets, and many immigrants. Combining studies on various types of pets with health information from different national and immigrant groups, combined with environmental studies in parks, streets, and sewage systems may provide some insights. Although such a focused study area may indicate a potential impact, it will not be representative for the general population, and may overestimate the potential effects.

Data collection for models

We suggest targeted development of the empirical data required to establish proper models by collecting data describing the AMR patterns found in pets and compare them with similar data from humans. Furthermore, we need to design studies that describe AMR patterns in meta-populations, consisting of pets within families and in close contact with the environment.

Model development

When more data have been collected, models should be developed that describe interaction patterns as social networks, and move into causal modelling to try to describe possible interventions in this complex system, possibly using directed acyclic graph (DAG)-based models or dynamic models.

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13 Appendix I

Table 13-1. Antimicrobial classes, agents and medicinal products marketed and used for dogs and cats in Norway. The list of specific human drugs which are also applied to animals is not available.

Antimicrobial class	Antimicrobial agent	Marketed in Norway	Animals used in (Dog, Cat)	Medicinal products specifically registered for veterinary use*	Medicinal products available for both human and veterinary indications	Comment
β-lactam	Amoxicillin	Y	D, C	X		Inj, tbl,
	Phenoxymethylpenicillin	Y	D, C		X	Tbl
	Benzylpenicillinprocain	Y	D, C	X		Inj
	Amoxicillin+clavulanic acid	Y	D, C	X		tbl, inj
	Ampicillin	Y	D, C		X	Infusion
	Cephalexin	Y	D, C	X		tbl
	Cephovecin	Y	D, C	X		Inj
Aminoglycosides	Dihydrostreptomycin	Y	D	X		Tbl
	Gentamicin	N	D, C		X	Mainly eye drops
Tetracycline	Doxycycline	Y	D, C	X		Tbl, mixture
	Oxytetracycline	Y	D, C	X		Powder
Sulphonamides and trimethoprim	Sulphadoxin and trimethoprim	Y	D			
Lincosamides	Clindamycin	Y	D, C	X		Capsules
Macrolides	Erythromycin	Y	D, C		X	Mixture
Quinolones	Enrofloxacin	Y	D, C	X		Inj, tbl
	Pradofloxacin	Y	D, C	X		Mixture, tbl

Antimicrobial class	Antimicrobial agent	Marketed in Norway	Animals used in (Dog, Cat)	Medicinal products specifically registered for veterinary use*	Medicinal products available for both human and veterinary indications	Comment
	Marbofloxacin	Y	D	X		Tbl
Combinations	Procainpenicillin, Dihydrostreptomycin	Y	D, C	X		Inj
	Diethanolamine fusidate, ramycetin sulphate, nystatin, prednisolone	Y	D, C	X		Ear drops
	Gentamicin, hydrocortisone aceponate, miconazole	Y	D	X		Ear drops
	Orbifloxacin, mometasone furoate, posaconazole	Y	D	X		Ear drops
	Polymyxin B, mikonazolnitrate, prednisolone acetate	N	D	X		Liniment for ear treatment
Others	Chloramphenicol	Y	D, C	X		Eye drops, ointment
	Fucidic acid (+bethamethason)	Y	D	X		Gel
	Fucidic acid	Y	D, C	x		Eye drops
	Metronidazole	Y	D, C		X	Infusion

*Closely related analogues are used in, and are of importance to, human medicine.

Table 13-2. Clinical isolates detected in pets in the period 1999-2013 (NORM-VET).

Clinical Isolates		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
***Staphylococcus* spp.**	Dogs	135	94		99		60				200				53*	201**
E. coli	Dogs						68				160					179 + 191***
Enterococcus* spp.***	Dogs						48									
Campylobacter	Dogs /cats		41													

* *S. schleiferi*

** *S. pseudintermedius*

*** ESBL/AmpC

**** *E. faecalis* and *E. faecium*

14 Appendix II – Exposure models

14.1 Social network models

Within a meta-population, specific structures exist. A common way to represent this in the context of infection spread, is to use social networks to illustrate the degree of contact between individuals (Christley et al., 2005; Enns and Brandeau, 2015; Zhu et al., 2015). A basic element in a social network is to describe whether the contact is more random, or, as typically the case for infectious diseases, as small world networks, as exemplified in Figure 14-1.

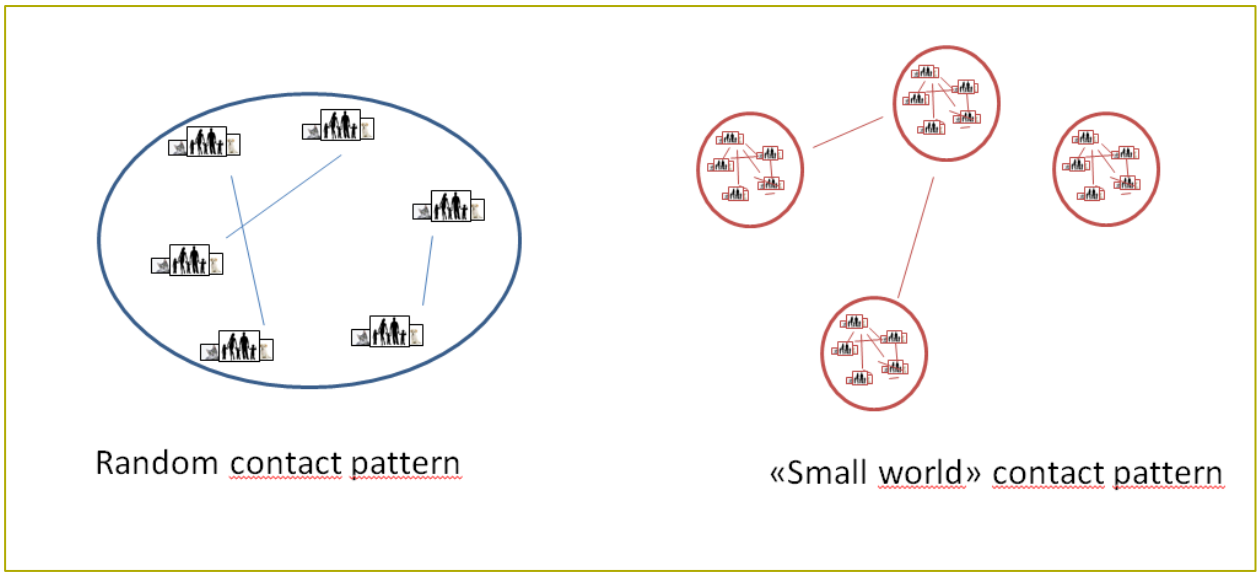


Figure 14-1 *An example of a social contact network model with a random structure (left) and a small-world contact network (right)*

The structure of the contact network is important in a control situation, as a small world network with hubs can be controlled by focusing on the hubs, whereas a more random network must be controlled using more general approaches to the whole population. For pets, hubs of importance will be imports, contact hubs at urban parks, animal kennels, shelters etc. A separated part of a network (right figure) may be more easily controlled than a connected part.

One question to be addressed for pets and AMR is whether the infectious links are connected, meaning that transfer from humans-to-animals and vice versa will represent unique reservoirs, or be occasional spill-over for which the long-term effect may be marginal. We may over-emphasize spill-over, as documented by similar clinical isolates, but then neglect more important pathways for control of this spread. Thus, if the pet-human route is considered to be spill-over, then the main aspect of control will be to limit introduction into

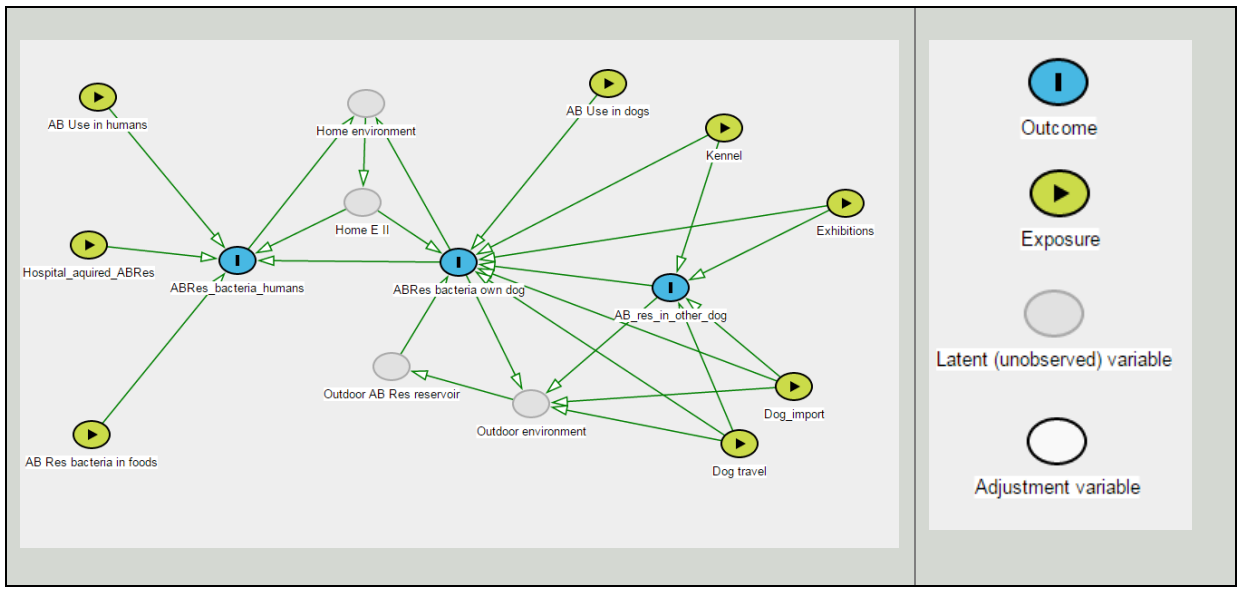
the pet “sink” of microbes and genes. If AMR transfer represents a main route, the situation is very different.

14.2 Causal models

If the aim of a risk assessment is to identify possibilities for intervention and control, a basic requirement is identifying causal pathways, in this context meaning ways to intervene in the chain of events leading to AMR within the human-pet relationship. Traditional risk assessment models using stochastic simulations also carry this assumption, but are not always distinctively expressed. Dynamic models with feedback structures also require the same.

Graphical causal models represent one method to start elucidating causal patterns. A technique using Directed Acyclical Graphs (DAG) is a development form of information theory, used in many fields where causal inference is essential (e.g., economy, social sciences, and epidemiology). The following simplified causal graph for dogs tries to capture the main factors of importance for transfer of AMR (via bacteria or genes) from dogs to humans. In the graphs in Figure 14-1, four classes of variable (outcome, exposure, non-observed or latent, or adjustment variable) are included. The green arrows represent causal pathways with directions.

One of the many uses of DAGs is to identify biasing paths, which are paths that may not be analysed as causal paths and therefore require other approaches. In the lower graphs, this is shown by changing the unobserved variable “Outdoor AB Res Reservoir” to an exposure node. Doing this, a number of arrows become red, impeding causal interpretations where the directions may be reversed – in practice leading into dynamic models.



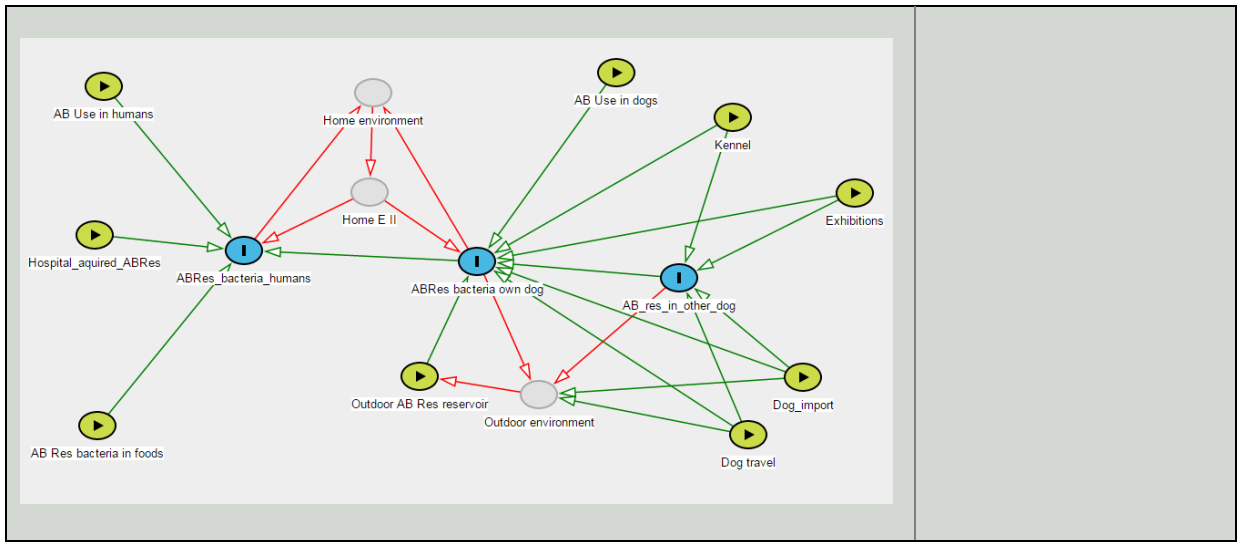


Figure 14-1 *A DAG model showing a possible basic model for establishing explanatory models in studying AMR within the human- pet relationships.*

The red arrows represent feedback structures, but mean that a DAG-based model is problematic as true causal models are only defined without feedback structures. One approach to using DAG-based models is to identify parts of causal networks where there is a directed causal pathway and focus on these pathways in describing potential interventions.

In this report, DAGs were used as a starting point for discussion on causal models, trying to place sound biological reasoning into more formal structures. Conceptual dynamic models were developed to illustrate the complexity of our assessments.

14.3 Dynamic models

By applying dynamic models, as typically used for infectious diseases, the feedback problem can be addressed, as feedback structures can be included. The most important difference, however, between the DAG model and the dynamic model lies in the fact that the causal web from a dynamic model with feedback cannot typically be analysed using standard statistical models. Adding to this complexity is the fact that environmental interactions introduce non-linearity into the model. Non-linear dynamic models can be used to produce scenarios, but with limited predictive capacity.

14.4 Stochastic risk assessment models, source attribution

Risk assessment models for AMR in pets have to be established using a set of models, as stated by Berendonk et al. (Berendonk et al., 2015). Traditional stochastic risk assessment models should be a part of this, but causal directed or dynamic models should also be used.

14.5 Special groups

Health workers, schools, and kindergarten teachers may be of special concern if pets constitute a problem for AMR introduction into families. Furthermore, it is unclear whether immunocompromised persons should take special precautions regarding pet ownership. These aspects are not part of the ToR and are not discussed further here.

15 Appendix III - Uncertainties – methodological aspects

Surveillance for AMR can either be passive or active, and the approach used will have a substantial effect on the prevalence of AMR determined. In passive surveillance, the number of isolates depends on samples submitted to the laboratories – it is possible that only samples from recurrent infections (already treated cases) or only samples from specific regions of the country might be submitted. Active surveillance tries to collect samples representative for the whole country, and with a sufficient sample size to enable comparisons over time. Monitoring the AMR situation over time within the veterinary sector requires sampling from many animal species and different types of foods. The sample size needs to be high enough to enable comparisons between the occurrence of resistance from year to year and the sample size is also affected by the target size of the differences that should be detected. The occurrence of resistance might be clustered within farms or flocks and, to avoid this effect, only one sample per herd or flock should be included in the surveillance. One isolate of the species may be picked at random from the agar (cultivation media) and be subject to susceptibility testing. The isolated bacterial species are normally tested for antimicrobial agents to which the “wild-type” population are totally susceptible. The substances included in the test panels might not always be those used in veterinary medicine, but are included because of their importance for human health and as indicators for special resistance forms.

Different tests can be used for the susceptibility testing, including: minimum inhibitory concentration / disc diffusion tests / gradient tests. The results from the different measurement approaches are not fully comparable. The platforms used should be standardised between laboratories in order to achieve comparable results. Also the definition of resistance can differ according to the purpose of susceptibility testing. Clinical breakpoints are used to define resistance in order to make the right decision on which a specific antimicrobial agent could be used for therapy, whereas the epidemiological cut-off values could indicate emerging resistance in the bacterial populations. This is more thoroughly described in the NORM/NORM_VET report 2013 and on the EUCAST homepage (www.eucast.org).

This results in an average prevalence of resistance for each bacteria species tested for each of the substances monitored in the country as a whole. However, as these isolates are picked at random, resistant isolates might not be selected despite being present. Emerging resistances presenting at very low levels in the total bacteria flora might thereby not be detected.

In order to identify emerging resistances at an early stage it is possible to screen selective for such resistances using selective media. Only the isolates that are resistant will then grow on these media, as the others will be suppressed. This methodology is much more sensitive for detecting low level, but emerging, resistances that are important to detect. However, the occurrence of such resistant bacteria (as for example /AmpC) in relation to the non-resistant counterpart must be quantified in order to reach conclusions on the burden of such emerging resistances.