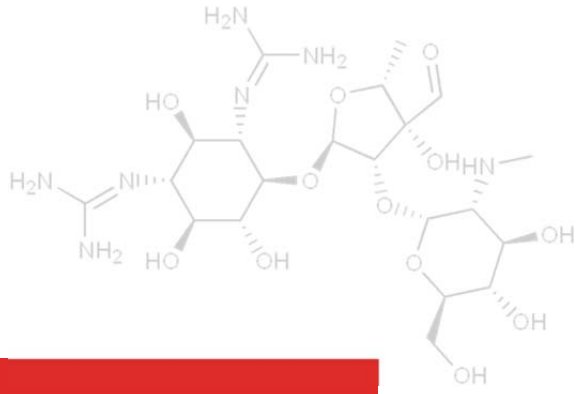
Veterinary Medicines Directorate



Antibiotic resistance and the responsible use of antibiotics in animals; what work is the VMD doing?

April 2016

Introduction

‘Antibiotics’ is a term used for antibacterials which are medicines essential for treating infections caused by bacteria in both people and animals. Antibiotics fall under the collective term of antimicrobials (this term also covers antivirals, antifungals and antiprotozoals). However, more commonly, when the term antimicrobial is used it is referring to antibiotics.

Bacteria naturally adapt and find new ways to survive the effects of an antibiotic, and this is accelerated by the use of antibiotics. The more you use antibiotics, the higher the risk that bacteria will develop resistance to it. Antibiotic resistance and the responsible use of antibiotics is a priority issue for government and one being taken very seriously.

Current scientific evidence suggests that occurrence of antibiotic resistance in animals is primarily as a result of antibiotic use in animals; similarly antibiotic resistance in people is primarily the result of antibiotic use in people. However, because there are a number of different ways that resistant bacteria can be transferred directly and indirectly between animals, people and the environment, it is clear everyone has a part to play.

The Veterinary Medicines Directorate (VMD) is the policy lead for government on antibiotic resistance in animal health and imputed into, and is committed to, the UK 5 year strategy on antibiotic resistance[1]. The strategy sets out three strategic aims to minimise the development of antibiotic resistance and protect human and animal health and welfare.

However, the work of the VMD regarding antibiotic resistance and the responsible use of antibiotics is not just limited to the ambitions of the strategy but is embedded into much of the day-to-day activity. The purpose of this document is to demonstrate this through four broad themes:

How we regulate what we have

How we gather evidence to shape the future

How we influence the bigger picture

How we engage with others

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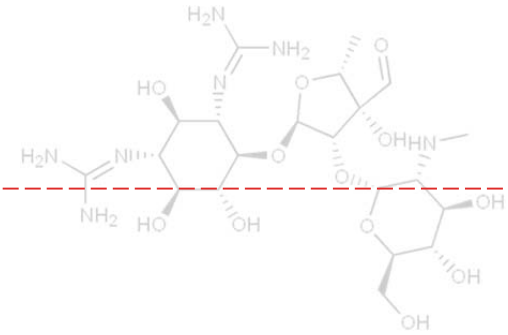
How we regulate what we have



1. Why is it important?

The manufacture, authorisation, marketing and distribution of veterinary medicines in all European member states are controlled by law through the European Commission's Veterinary Medicinal Products Directive[2]. This directive provides the basis for the UK's Veterinary Medicines Regulations (VMR) which set out our national controls.

Through these laws we can ensure that:

- antibiotics available for animals are of consistent and high quality;
- we minimise the presence of fake or illegal products that may be ineffective;
- accurate information is accessible by prescribers and users;
- access to these vital medicines is subject to effective, professionally guided, stewardship.

2. Availability

An antibiotic for animal use in the European Union (EU) becomes available after being authorised through one of three application routes chosen by the veterinary pharmaceutical company:

1. nationally: medicine is authorised by the national competent authority of chosen country for use in that country only - in the UK the national competent authority for medicines for use in animals is the VMD;
2. decentralised: medicine is simultaneously authorised by national competent authorities in a number of EU countries selected by the applicant, for use in those countries;
3. centralised: medicine is authorised by the European Medicines Agency for use in all EU Member States and the European Economic Area.

To authorise a medicine, the VMD carries out a detailed scientific assessment of the data submitted by a veterinary pharmaceutical company to ensure that the medicine fully satisfies three criteria: safety, quality and effectiveness.

Safety makes sure that the antibiotics we authorise are safe for the user, the consumer and the environment. This will include:

- assessing the toxicology of the product - understanding whether, and how the chemicals in the medicine could cause adverse reactions in the target species or in people, taking into account the way these chemicals cause changes to the normal biological functions of the body;
- setting a withdrawal period, if the antibiotic is to be used in a food-producing animal - this is the minimum length of time after treatment that must pass before an animal may go for slaughter or have its products, such as milk or eggs, considered to be safe for consumers.

Quality makes sure that the antibiotics we authorise are manufactured to the high standard required. This will include ensuring that the applicant has demonstrated:

- the antibiotic molecule is manufactured appropriately;
- the manufacturing process delivers a reproducible product;
- the medicine will perform as it should up to its expiry date.

Effectiveness makes sure that the antibiotics we authorise will work against the bacteria causing illness in all of the animals the medicine is authorised to treat. This will include ensuring that the applicant has demonstrated:

- that antibiotic resistance has been taken into account;
- that a correct dosage regimen has been set - how much, how often and for how long;
- that responsible use of antibiotics warning is on the product literature and data sheet (Summary of Product Characteristics).

3. Access

All antibiotics for animal use in the UK are classed as 'prescription only medicine' (POM-V), and therefore can only be prescribed by a veterinary surgeon to animals under their care following a clinical diagnosis. It is down to the professional judgment of the veterinary surgeon whether an animal, or a particular group of farmed animals, requires such treatment. The requirement to use antibiotics responsibly forms part of the Royal College of Veterinary Surgeons Code of Professional Conduct for Veterinary Surgeons[3].

Antibiotics can be given to animals in different ways. One method is by mixing the medicine into their food, creating a medicated feed. Feed mills and farmers that manufacture medicated feed must be approved by the VMD in Great Britain, or the Department of Agriculture & Rural Development in Northern Ireland. Antibiotics for use in animal feed, also known as antibiotic premixes, require a Medicated Feedingstuff prescription (MFSp) from a veterinary surgeon. A veterinary surgeon may only issue an MFSp following a clinical assessment of the animals, and the animals must be under the vet's care. To ensure compliance, inspections of medicated feed manufacturers are carried out.

4. Good practice

Veterinary Surgeons can only dispense antibiotics from premises that are registered as a Veterinary Practice Premises with the Royal College of Veterinary Surgeons (RCVS). All registered premises are regularly inspected, either by RCVS inspectors if the practice is registered under the RCVS Practice Standards Scheme, or by the VMD's inspectors if not.

The VMD also has an inspection team who is responsible for inspecting manufacturing sites exclusively producing veterinary medicines in the UK and third countries, and inspecting veterinary-only wholesale dealers in the UK. This is to ensure sites comply with European Directives and the Veterinary Medicines Regulations that apply to the manufacture and supply of veterinary medicines on the UK market.

5. Illegal use

The VMD inspects premises in the UK that manufacture, distribute and supply veterinary medicines, including internet retailers, to ensure they comply with the Veterinary Medicines Regulations.

In addition, the VMD's Enforcement Team acts on complaints received about internet retailers. The enforcement team has built good working relationships with key internet retail sites.

In response to concerns about the increase in the number of internet retailers, and the extent to which they comply with the VMR, VMD launched an Accredited Internet Retailer Scheme (AIRS)[4] in 2012. Whilst the majority of websites based in the UK are run by qualified professionals, there is always the risk that some sites will breach the VMR by selling veterinary medicines:

- without the advice of a veterinary surgeon, pharmacist or Suitably Qualified Person
- that are not authorised for use in animals in the UK

AIRS is a voluntary scheme and a means of facilitating self-regulation by UK based internet retailers supplying veterinary medicines. The scheme gives animal owners greater assurance that they are buying authorised veterinary medicines on the internet. All internet retailers that have been accredited are able to display the following logo on their site:

For added assurance the logo includes an ID number which is unique to that retailer. Clicking the logo on the retailer's website will take you to a VMD website confirming the site name and details associated with that ID.

How we gather evidence to shape the future

1. Why is it important?

We need to understand the problem - what increases resistance, what motivates different prescribing habits, which antibiotics are being used and for what? To gain a better understanding, the VMD is taking steps to gather evidence which will help inform measures to preserve these vital medicines for the future.

2. Research

The VMD funds a small portfolio of research projects which are designed to increase understanding of the development of antibiotic resistance. These include examining the ways in which resistant bacteria or resistance genes are transmitted, and investigating the factors which influence prescribing patterns.

3. Data on quantity of veterinary antibiotics sold

The VMD collects and publishes annual figures on UK sales volumes of antibiotic active substances in medicines authorised for use in animals[5]. These reports are based on sales data provided by veterinary pharmaceutical companies - initially this was voluntary, but from 2005 it has been a legal requirement.

Sales data do not permit accurate analysis of antibiotic consumption by animal species or production category and in general overestimates use, as not all antibiotics sold will be used. The limitations of sales data and the need for more accurate antibiotic consumption data are fully recognised.

The VMD also participates in the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, which collects information on how antibiotics are used in animals across the EU.

4. Collecting antibiotic usage data from farms

The VMD has developed a central data hub to host data on antibiotic use in UK livestock sectors. The system is currently being tested and will be compatible with systems for collecting data on antibiotic usage which are under development on a voluntary basis by the priority species sectors (poultry, pig and cattle sectors).

The VMD central data hub will not contain information on the reason for treatment with antibiotics as data will be collated by the hub at an aggregated level, by species and farm type or commodity sector. However, the systems at industry level are being developed to collect data on farm level use, and the addition of data fields to capture “reason for treatment” are being discussed.

Data may come from farm or veterinary practice records. This may vary between species sectors depending on the type of voluntary system they develop, though in each case data will need to pertain to individual farm usage. Data will be disaggregated by species (and farm type or commodity sector within each of the priority species, i.e. broilers vs other meat poultry vs layers; dairy vs beef cattle) and by antibiotic product, from which active ingredient can be derived.

5. Monitoring bacteria for resistance to antibiotics

In addition to reporting sales data, the VMD monitors levels of antibiotic resistance in bacteria isolated from animals. This is carried out in two ways:

1. EU Harmonised Monitoring

   In line with EU legislation, the VMD collaborates with government laboratories to test for antibiotic resistance in bacteria of animal origin which are of importance to human health. Bacteria such as *Salmonella* and *Campylobacter*, which are common causes of gastro-intestinal upset or ‘food-poisoning’ in people, are monitored for resistance to key classes of antibiotics. The sampling framework and strategy is defined in the EU legislation and designed to investigate antibiotic resistance in a representative number of bacteria per year from the key livestock populations (e.g. pigs, poultry) in each EU Member State.

2. Clinical Surveillance

   The VMD funds the antibiotic resistance testing of bacteria which are isolated through the Animal and Plant Health Agency's (APHA) clinical surveillance scheme. Under this scheme, private vets and farmers can send in clinical samples and carcases to APHA laboratories for testing. This surveillance is helpful in identifying antibiotic resistance in veterinary pathogenic bacteria which may be present in animal populations in low numbers.

Antibiotic resistance data for the UK are submitted to the European Food Safety Authority (EFSA)[7] for inclusion in the annually published EU summary report on 'antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food'[6]. Additionally, in 2015 it was published for the first time in the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report[8]. The VMD also presents the UK's antibiotic resistance data in the annually published Veterinary Antibiotic Resistance and Sales Surveillance (VARSS)[5] report.

In addition, the UK is leading the Target Pathogen Monitoring Programme which is an EU wide initiative to establish a common surveillance scheme for antibiotic resistance in veterinary bacteria which cause disease in animals.

6. Residues of antibiotics in food

Before any veterinary medicine is authorised for use in food-producing animals, tests are carried out to set conditions on its use to ensure that should any residue of that medicine be in food it will pose no health risks for consumers.

The European Medicines Agency[9] assesses toxicological data to establish what concentration of a particular residue is considered to be safe for consumers in meat or other animal products. This statutory limit is called the Maximum Residue Limit (MRL).

The VMD then assesses how long it takes after the end of treatment with a particular medicine for any residues in food from the treated animal to fall below the set MRL. From this, a withdrawal period is set as one of the conditions of use for the medicine – this is the minimum length of time after treatment that must pass before an animal may go for slaughter or have its products, such as milk or eggs, taken for human consumption.

In Great Britain over 30,000 samples are taken annually at slaughterhouses and on farms, which cover cattle, sheep, pigs, horses, poultry, wild and farmed game, farmed fish, milk, honey and eggs.

Under EU law, the VMD manages an extensive statutory surveillance programme through testing of samples to ensure compliance with set limits.

The samples are tested for a range of unauthorised and authorised substances including antibiotics. Where residues are detected a follow up investigation is carried out at the farm of origin to establish the cause of the residue. Results of investigations show that residues of authorised substances are usually due to medicines not being used in accordance with their instructions.

7. Suspected adverse events

All medicines, including antibiotics, have the potential to cause harmful and unintended reactions even when the medicine is given at its correct dose and duration. Also, sometimes a medicine might not work as expected. If either of these situations occurs, they are referred to as suspected adverse events. The VMD records and monitors all reported adverse events that have involved an animal medicine[10].

Where emerging issues are clinically and statistically significant, the VMD's Pharmacovigilance Unit determine how these risks can be best managed. Usually this will involve the addition of warnings to the medicines data sheet and labels. However, if more serious problems are identified the VMD has the power to remove the product from the market permanently, or until further studies confirm how the product can be used safely.

How we influence the bigger picture

1. Why is it important to think big?

We know that the VMD must have a voice within the groups that have influence in developing policies, legislation and guidelines on issues that will improve the safe and effective use of antibiotic medicines.

This includes ensuring that any changes in the availability of antibiotics, or the way in which they are regulated in animal health, are carefully considered and based on scientific evidence. This includes weighing up the potential impact on public health, animal welfare, or the clinical freedom of veterinary surgeons to use their professional experience to make prescribing decisions.

2. The European Commission

The European Commission is the European Union's executive body. It represents and upholds the interests of the EU as a whole. It drafts proposals for new European laws and manages the day-to-day business of implementing EU policies and spending EU funds. The Commission is influenced by opinion and outputs from a number of key organisations and groups within the EU including:

- European Medicines Agency - an agency of the European Union responsible for the scientific evaluation of both human and animal medicines developed by pharmaceutical companies for use in the European Union;

- European Food Safety Authority - a European agency funded by the European Union that operates independently of the European Commission and EU Member States. It was set up in 2002 following a series of food crises in the late 1990s to be a source of scientific advice and communication on risks associated with the food chain;

- Heads of Medicines Agencies - a network of the Heads of the National Competent Authorities whose organisations are responsible for the regulation of medicines for human and veterinary use in the EU.

How the VMD engage with the EU

In 2013 the Commission, as part of their 'Action plan against the rising threats from Antimicrobial Resistance'[11], made a request to the EMA asking for scientific advice around four areas relating to antibiotics. To respond to this the EMA formed the Antimicrobial Advice ad hoc Expert Group (AMEG), bringing together a number of representatives and experts from various EU scientific veterinary and human groups including from the VMD. The AMEG's report, which addressed the impact of antibiotic use in animals on public and animal health, was finalised at the end of 2014[12].

Following a further request from the Commission, by the end of 2016, the EMA and EFSA will give scientific opinion on measures to reduce the need to use antibiotics in animals in the EU, and the resulting impacts on food safety.

In 2010, the HMA published a 'Strategic Plan on Veterinary Antimicrobial Issues'[13]. Following this the HMA established the Antimicrobial Resistance Veterinary Task Force to help develop an action plan on antimicrobial issues and oversee its delivery. The VMD, representing the UK, are chair and secretariat to this task force.

3. Guidelines on data requirements for application

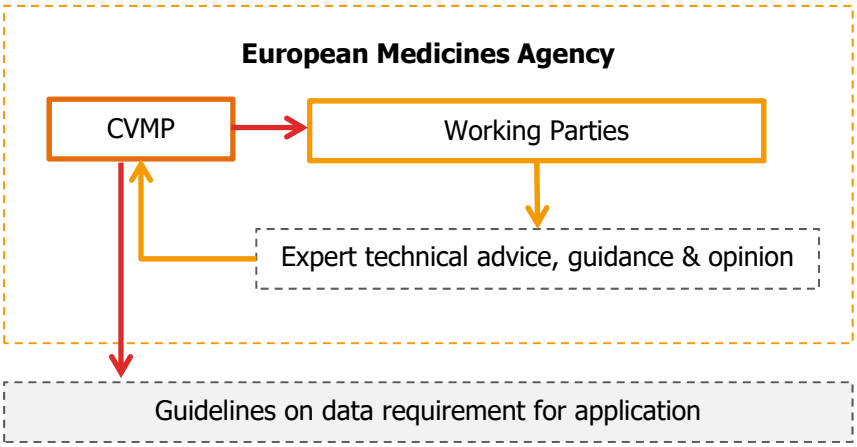
Within the EU to apply for an authorisation for a medicine containing an antibiotic, a veterinary pharmaceutical company must submit a large amount of supporting evidence to demonstrate that the benefits of the product outweigh the risks. Many of the technical requirements for this evidence are set out in guidelines, which then become a standard with which to comply.

To contribute to the content of these guidelines by having representatives on the following committees and working parties:

Committee for Medicinal Products for Veterinary Use (CVMP) is a committee which has scientific experts representing each member state. The committee meets at the European Medicines Agency and is responsible for preparing opinions on complex applications for medicines for veterinary use.

The CVMP establishes working parties to consult on specific scientific issues - these groups are made up of members with expertise in a particular scientific field and they provide advice, guidance and opinion. Working parties which have a VMD representative include:

- Antimicrobials Working Party
- Efficacy Working Party
- Environmental Risk Assessment Working Party
- Inspectors Working Party
- Pharmacovigilance Working Party
- Quality Working Party
- Safety Working Party
- Scientific Advice Working Party



Examples of guidelines from CVMP relating to antibiotics are:

- Revised guidelines on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005);[14]
- Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev1).[15]

VICH is a trilateral (EU-Japan-USA) programme aimed at producing guidance to harmonise the technical requirements for pharmaceutical companies wishing to apply for a Marketing Authorisation for a veterinary medicine, with the ambition that pharmaceutical companies can produce one set of data that will satisfy all territories.

In December 2004, the VICH published guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (VICH GL27)[16].

4. International regulatory authorities

VMD regularly speaks with the veterinary regulatory authorities in Australia, New Zealand, USA and Canada, and have cooperation agreements set up with them.

How we engage with others

1. Why is it important?

To tackle antibiotic resistance and promote responsible use, a societal change is required; government alone cannot make the difference. It is important that VMD is proactive in raising awareness and takes time to learn from others about the barriers and challenges they are facing. To do this we have set up a number of initiatives to engage and communicate with a wide range of interested parties, and to facilitate communication between them.

2. Publicity stands

Since 2009 the VMD has taken an exhibition stand to a wide variety of shows and events up and down the country, speaking to pet owners, veterinarians, veterinary nurses, pharmacists, farmers and pharmaceutical companies. VMD staff with a wide range of expertise, usually including a vet, answers questions from visitors to the stand, hands out literature and demonstrates aspects of our website. The responsible use of antibiotics is one of the main topics promoted at events attended.

3. Sector engagement groups

VMD has established a number of species specific engagement groups: pig, poultry, cattle, companion & equine, fish and camelid & small ruminant. Each group meets annually and consists of members who represent a broad spectrum of interest and influence within their sector. Members include: specialist veterinary surgeons, farmers, academics, retailers, industry bodies, trade associations and animal health charities. These groups are an opportunity for open and honest dialogue to raise awareness and discuss antibiotic use and issues around antibiotic resistance.

4. Lectures & presentations to students and professionals

The VMD's Antimicrobial Resistance team has an outreach and education programme that aims to engage more closely with those who look after animals, or who are part of the livestock and food industries. This programme encourages open communication and raises awareness about practices and initiatives that impact on the development of resistance. They give lectures and presentations in many different forums including veterinary colleges, retail and farming meetings and other key industry events.

5. Antibiotics awareness initiatives

European Antibiotic Awareness Day (EAAD)[17] and World Antibiotic Awareness Week (WAAW)[18] are annual initiatives that take place on the 18 November, and the third week of November of every year. Their aim is to raise awareness about the threat of antibiotic resistance and to promote the prudent and responsible use of antibiotics.

The VMD uses these initiatives to work alongside others in the animal health sector to promote the responsible use of antibiotics and raise awareness through animal health publications and social media.

6. Events & conferences

The VMD looks to support events and conferences which aim to raise awareness around antibiotic resistance and promote discussion around the issues. This can be achieved through a number of ways: sponsorship, providing speakers, chairing sessions, etc.

7. Guidance

To help give guidance on specific issues the VMD have published the following on gov.uk:

- Responsible use of animal medicines on the farm (which includes use of antibiotics)[19]
- Responsible antibiotic use under the prescribing cascade[20]
- LA-MRSA: information for people who work with livestock[21]

References and Links

1. UK 5 year strategy on antibiotic resistance
   https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018
2. European Commission's Veterinary Medicinal Products Directive
   https://www.gov.uk/guidance/veterinary-medicines-regulations
3. Royal College of Veterinary Surgeons Code of Professional Conduct for Veterinary Surgeons
   http://www.rcvs.org.uk/advice-and-guidance/code-of-professional-conduct-for-veterinary-surgeons/
4. Accredited Internet Retailer Scheme (AIRS)
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5. Veterinary Antibiotic Resistance Surveillance and Sales (VARSS) report
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6. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report
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7. European Food Safety Authority (EFSA)
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8. Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report
   http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-JIACRA-report.pdf
9. European Medicines Agency (EMA)
   http://www.ema.europa.eu/
10. Report a Suspected Adverse Event
    https://www.gov.uk/report-veterinary-medicine-problem
11. Action plan against the rising threats from Antimicrobial Resistance
    http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf
12. AMEG and recommendations on the use of antibiotics in animals
    http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000639.jsp
13. Heads of Medicines Agencies Action Plan on Antimicrobial Issues
    http://www.hma.eu/tfvetantimicrobialissues.html
14. Revised guidelines on the SPC for antimicrobial products
    http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/02/WC500070670.pdf
15. Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances
    http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500200984.pdf

16. Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (VICH GL27)
http://www.vichsec.org/guidelines/pharmaceuticals/pharma-safety/antimicrobial-safety.html
17. European Antibiotics Awareness Day
http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx
18. World Antibiotics Awareness Week
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19. Responsible use of animal medicines on the farm
https://www.gov.uk/government/publications/responsible-use-of-animal-medicines-on-the-farm
20. Responsible antibiotic use under the prescribing cascade
https://www.gov.uk/guidance/responsible-antibiotic-use-under-the-prescribing-cascade
21. LA-MRSA: information for people who work with livestock
https://www.gov.uk/government/publications/la-mrsa-information-for-people-who-work-with-livestock

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Streptomycin

Fluoroquinolone

Cephalosporin

Penicillin