Prevention Is Better Than Cure

Lucie Pokludová

Abstract

Preventive measures and health programmes should help significantly to keep animals healthy. If animal welfare principles and good animal husbandry practices are also followed, minimal or no use of antimicrobials can be, with high probability, achieved. Setting priorities in biosecurity, which fits exact conditions of farm/husbandry is vital. Thorough mechanic cleaning, rational use of disinfection, disinsection and deratisation, proper ventilation and keeping the proper temperature and humidity contribute to keep good environment both in old stables and hi-tech husbandries. Health programmes, including vaccination tailored for local conditions, animal species and technologies used in the respective husbandry should be defined by educated veterinarians, specialised not only on treatment, but also on preventive medicine, use of alternatives to antimicrobials and management. Close cooperation of vets, farmers and people taking immediate care of animals and facilities is the basic prerequisite of the effectivity of such system. Therefore, tools for motivation and socio-economical aspects also belong among the key elements for effective preventive measures, which finally can help to minimise or skip the use of antimicrobials and help to combat antimicrobial resistance.

Keywords

Preventive medicine · Health programmes · Vaccination · Biosecurity · Hygiene · Good husbandry practices · Animal welfare · Disinfection · Disinsection · Deratisation · Alternatives to antimicrobials · Socio-economical aspects of prevention

1 Prevention Is Better Than Cure

The concept that “prevention is better than cure” (P>C) in veterinary medicine or agricultural sector generally should be understood in its complexity. Even holistic and integrated approach is necessary for the performance of this “P>C concept”, primary target is to keep animals in good health and welfare status. As pointed out by the European Commission (2015) Guidelines for the prudent use of antimicrobials, preventing infections in the first instance is the best way to achieve reduction of consumption of antimicrobials, through minimising the need to use antimicrobials, as reducing the number of infections reduces the number of treatments needed. The “P>C concept” is fully in line with the new Animal Health Strategy according to European Commission (2014).
The objective of reducing the use of antimicrobials is also in line with animal welfare, aims to reduce the density of the farm animal population and might be to do “step back” in intensity of the farming production, going more close to natural biological characteristics of the animals. That can be seen on the first side as step back also in economical parameters, but it could be compensated by lower costs of veterinary care on diseased animals as well as higher price purchase of better quality products from the healthy and sustainable husbandries. Overstocking is believed to be one of the major risk factors in the emergence and spread of infections that require the use of antimicrobials to reduce the suffering of sick animals (European Commission 2015).

There is a broad spectrum of medical and non-medical factors and drivers influencing antimicrobial usage in food-producing animals. One of other key factors, that can be considered across different livestock sectors, is the herd health status that significantly influences the need for antimicrobial treatments. Considering the real farm practice view, the observation of changes in feed and water intake by the animals as well as clinical signs was reported as the main driver for farmers to ask veterinarian to initiate an antimicrobial treatment (Friedman et al. 2007). Gastrointestinal disorders in young animals can be considered as one of the most frequent reasons for prescribing antimicrobials (for group/herd medication) among different sectors (piglets in the weaning period, broiler chickens and calves). Among other very frequent reasons belong respiratory clinical signs (beef calves/cattle and pig fatteners and turkeys, in less scale in broiler chickens). Reproductive clinical signs in sows and in cows are also of importance when considering frequency of antimicrobial prescription (De Bryine et al. 2014; FVE 2016a, b; Jensen et al. 2014; van Rennings et al. 2015).

There are also non-medical drivers. Those considered technical as herd characteristics, such as farm size, production type or management (e.g. farrowing rhythm, calves housing, oestrus synchronisation), biosecurity level were shown to be significantly associated with the amount of antimicrobials used in a herd (Fertner et al. 2015; Postma et al. 2016). However, social and behavioural factors, as interplay, cooperation, teamwork and professional relationship among farmers and veterinarians, including attitudes and habits towards responsible use of antimicrobials as well as economical drivers also plays a significant role (Coyne et al. 2016, 2018; Moreno 2014). Once framers are couched and start to believe they could use other means than antimicrobials to keep animals healthy and that the farms are still doing well and are in good productivity condition, they will not go back to the practices of overuse of antimicrobials. Educated farmers aware of antibiotic policies as well as those perceived higher risk of using antimicrobials also had lower actual antimicrobial usage (Visschers et al. 2016). The results of Scherpenzeel et al. (2017) show that it is more likely that broiler farmers who use a low amount of antibiotics for their broilers perceive more control and less risk and uncertainty with regard to the reduction of antibiotics use than high users. Uncertainty as driver for antibiotics use is mentioned as well in dairy farming with regard to the prevention and treatment of mastitis (Swinkels et al. 2015). Trujillo-Barrera et al. (2016) found that perceived risk appeared to be a barrier to the adoption of sustainable practices, while risk tolerance appeared to be a positive moderator of the relationship between economic rewards and adoption.

Animal husbandry and disease prevention measures that can be implemented to improve animal health and welfare can be divided into three main categories [modified according RONAFA report (EMA and EFSA 2017)]:

**Primary prevention category** includes practices reducing the introduction and spread of microorganisms/diseases between farms. There should be implemented principles of external biosecurity, performed compartmentalisation and eradication measures.

**Secondary prevention category** includes practices to reduce transmission or spread of microorganisms/diseases within a farm. There should be implemented principles of internal
biosecurity and properly performed groupings of production. Appropriate housing design, building and maintenance. 

**Tertiary prevention category** should be targeted on increase of the ability of animals to cope with the infectious disease causative pathogens: proper housing, well-balanced nutrition and improved feed strategies, reduction of stress, farm health plans including vaccination programmes tailored for the farm conditions and epidemiological situations, early diagnostics including tools like smart farming as well as genetic selection are necessary prerequisites to keep good health status of the herd/flock. Care should be taken both at individual, and also group of animals/herd/flock level.

Despite the fact that the antimicrobials seem to be still the only powerful tool for the treatment of acute diseases, there are some alternatives available to antimicrobials (*Note: author think that should be rather called “alternative tools”*), that could be used as preventive care/treatment before onset of clinical signs, or e.g. in cases where it is expected that some stressful conditions make animals prone to be sick. Among these alternative tools (Table 5) belong (non-exhaustive list): prebiotics, probiotics, “competitive exclusion” products (i.e. excluding pathogenic bacteria from the host by competition with innocuous bacteria) (Callaway et al. 2008), bacteriophages, immunomodulators, phytotherapeutics (including etheric oils and mixtures of extracts, tinctures and others), organic acids, vitamins, minerals although data are generally lacking about their efficacy, feasibility and return on investment (Collineau 2016; EMA and EFSA 2017).

An expert elicitation conducted among 111 European pig health experts identified improved internal biosecurity, external biosecurity and housing conditions as the alternative measures with the highest perceived effectiveness, whereas increased vaccination, increased use of anti-inflammatory products and improved water quality were reported as having the highest feasibility (Collineau 2016). The highest perceived return-on-investment was reported to be associated with improved internal biosecurity, use of zinc/metals and increased diagnostics to develop disease control action plans for pig farms (Postma et al. 2016). In other sectors (poultry, cattle), other factors can be considered of bigger importance and once improved—e.g. in the poultry sector 1-day-old chickens’ quality, appropriate temperature and humidity, slower growing of chickens, lower density (decrease of ammonium)—can help significantly to reduce the use of antimicrobials (ASOA 2017). In dairy cattle sector EFSA (2009) in its scientific opinion on farming systems has stated that “the farming system by itself is a major factor determining the health problems of dairy cattle” and “the genetic component underlying milk yield has also been found to be positively correlated with the incidence of lameness, mastitis, reproductive disorders and metabolic disorders” and in beef cattle/veal with high use of antimicrobials according to Catry et al. (2016) were respiratory diseases linked to overstocking, inadequate ventilation, mixing of animals and failure of early diagnosis and treatment. So solving these issues in dairy and beef cattle can be a proactive solution instead of reactive approach with high usage of antimicrobials.

If the vast majority of the above-mentioned solution approaches is implemented and on the other hand wrong practices and (extremely) high intensity of farming are avoided, the animals will be less stressed, well cared and there can be expected increase of ability of an animal’s immune system to respond appropriately to an infectious challenge helping to keep animals healthy.
2 Biosecurity and Hygiene

According to the “Animal Health Law” (Regulation (EU) No 2016/429) biosecurity is defined as the sum of management and physical measures designed to reduce the risk of the introduction, development and spread of diseases to, from and within an animal population or an establishment zone, compartment, means of transport, premises or location.

Locally tailored biosecurity plans that identify potential pathways for the introduction and spread of disease in a zone or compartment, and describe plan and performance of the measures that are being or will be applied to mitigate the disease risks should be in current time common practice of each farm. Biosecurity plans are also in accordance with the recommendations in the OIE Terrestrial Code (OIE 2013).

There are two cornerstones of the biosecurity: EXTERNAL pertains the introduction of the pathogen to the population of animals kept in some unit (can be understood as, e.g. country or farm) and INTERNAL targets reduction of the spread of pathogen within the population of animals kept in the respective unit.

FAO (2010) considers three main elements of biosecurity:

1. Segregation
   The creation and maintenance of barriers to limit the potential opportunities for infected animals and contaminated materials to enter an uninfected site. When properly applied, this step will prevent most contamination and infection.

2. Cleaning Materials
   (e.g. vehicles, equipment) that have to enter (or leave) a site must be thoroughly cleaned to remove visible dirt. This will also remove most of the pathogens that contaminate the materials. Mechanical cleaning (water and brush as well as high-pressure washer (110–130 bar, or where appropriate with hot water/steam) are efficient tools not introducing any chemical co-selectors of resistance.

3. Disinfection, e.g. according to the OIE Terrestrial code (OIE 2014)
   When properly applied and proper actives selected, including rotation to ensure efficacy and minimise/avoid resistance, disinfection will inactivate any pathogen that is present on materials that have already been thoroughly cleaned.

Speaking about biosecurity in connection with the reduction of need to use antimicrobials, mostly the unit is understood as farm (herd/flock) and the farm owner or manager is responsible for the setting of a biosecurity system.

For epidemic notifiable infections, as considered also by Animal Health law, the competent authority of the respective country/or e.g. the EU is in charge of the necessary biosecurity measures nationally and internationally, and outbreak measures. Those measures include banning import and other protective measures to avoid introduction of any animals/products that can cause introduction/spreading of the epidemic agent such as checking of imported animals and sources they are coming from, inspections, surveillance, check of the animals/products on the market and at the slaughterhouse level.

There should also be considered different routes of transmission (see Table 1) and their “rate of importance” in the transmission of the exact diseases altogether with combination of the probability of transmission and frequency of occurrence of transmission routes taking into account also certain pathogens/diseases incidence in the source of transmission.
| Route of transmission | Examples of vehicles and vectors | Example of pathogens | Notes |
|------------------------|---------------------------------|----------------------|-------|
| Direct contact among animals and their secretions | Body fluids (urine, faeces, secrets/saliva, milk, blood) | All pathogens, of high importance e.g. MRSA (Staphylococcus aureus resistant to methicillin) | Not only clinically diseased animals to be considered as source, use screen methods for carriers investigation. |
| Breeding (mother to piglets) | | | Entry into the susceptible animal through contact with the mucous membranes, such as the eyes, nose or mouth. |
| Perinatal (mother giving birth) | | | |
| Tissues (e.g. skin lesions) | | | |
| Aerogenous transmission (longer distance) | Small dust particles, air flow | Mycoplasma pneumoniae | High level of risk even for distance about 4 kilometres, high biosecurity level farms with air filters/conditioning |
| Aerogenous transmission (within the housing) | Coughing, sneezing, aerosol droplets, small dust particles | Actinobacillus pleuropneumoniae | Most microorganisms are not able to survive for extended time periods - close proximity of infected and susceptible animals is required for disease transmission. Aerosol transmission can also occur when infected droplets from urine, faeces, or birthing material get stirred up from contaminated surfaces/dust and inhaled. |
| Staff | | | Adequate ventilation, ammonium decrease, dust minimisation |
| Vehichles, equipment | Needles, balling guns | Actinobacillus pleuropneumoniae, Streptococcus suis | Proper cleaning, disinfection, where possible use e.g. needle free delivery devices |
| – Buckets (feed/water) | | | |
| – Bedding, shovels | | | |
| – Vehicles, trailers | | | |
| – Boots/clothing | | | |
| Feed | | Salmonella spp. | |
| Water | | All bacteria, yeasts, algae participating in biofilm | |

(continued)
2.1 External and Internal Biosecurity

2.1.1 External Biosecurity Subcategories

1. Purchasing policy:
   (a) Animals preferably from one source/same supplier:
       (i) Avoid mixing of sources
       (ii) If necessary, minimum number of sources with same health status/vaccination status is preferred (this can be difficult for some species, e.g. calves)
   (b) Semen and embryos from reputable sources/health status declaring
   (c) Routine cleaning and disinfection of means of transport, prior to transport checks:
       (i) Boxes/containers, trucks, lorries, boats should be properly cleaned and disinfected (e.g. in pigs evidence that ASF, *Actinobacillus pleuropneumoniae*, TGE and

| Route of transmission | Examples of vehicles and vectors | Example of pathogens | Notes |
|-----------------------|---------------------------------|----------------------|-------|
| Manure and bedding    |                                  | *Salmonella* spp., *Campylobacter* spp., *Enterobacteria* (including ESBLs/AmpC, mcr- genes carriers), *Enterococci*, *Mycobacterium (tuberculosis, avium)*, *Brachyspira* spp. | Potential to survive differs across different pathogens and is highly dependent on the environmental conditions (rather cold/vet support survival, drying/hot do not support) |
| Rodents, birds, bats, wild animals, domestic animals | Most frequently birds | *Bordetella* spp., *erysipelas*, avian tuberculosis | |
| Rodents               |                                  | *Atrophic rhinitis Pasteurella multocida* alone or in combination with *Bordetella bronchiseptica*, *E. coli* diarrhoea, *Streptococcus suis*, leptospirosis, salmonellosis, *Brachyspira* spp., rotaviral diarrhoea, *PRRS* | |
| Wild boars            |                                  | Classical Swine Fever and African Swine Fever | |
| Flies and other insect vectors |                                  | *Enterobacteria* (including ESBLs/AmpC, mcr- genes carriers), *Streptococcus suis* | |
| Semen                 |                                  | Most bacterial contaminants of semen are from faecal/environmental contamination. | |

Table 1 (continued)

| Route of transmission | Examples of vehicles and vectors | Example of pathogens | Notes |
|-----------------------|---------------------------------|----------------------|-------|
| Semen                 |                                  |                      | Most bacterial contaminants of semen are from faecal/environmental contamination. | Semen collection and distribution and hygiene in all steps seems therefore critical, together with routine screening of breeding females for semen-spread infections. |
Streptococcus suis can be spread by contaminated vehicles).

(i) For 1-day-old poultry it is extremely important to check for proper working of the all fans in the transport vehicle/truck, cleaning/changing of filters, checking the heaters and air ventilation/circulation, checking if proper humidity can be ensured during the transport to avoid stress making the poultry prone to disease.

(ii) Avoid/minimise use of litter, enrichment materials or feed ingredients originating from other farms, as they increase the risk of pathogen transfer.

(iii) Ensure proper water sources during the transport.

(iv) Avoid any interfering “risky contacts”.

(d) Health status documented

(e) Quarantine period

(i) Isolate the animals with signs of sickness.

(ii) Ensure personnel hygiene and disinfection, changing the boots/clothes.

(f) Following the rules stipulated by competent authorities of country, regional authorities

2. Rules for removing:

(a) Animals

(b) Manure and slurry

(c) Bedding (Ensure that appropriate disposal of soiled bedding is carried out in order to prevent the spread of diseases)

(d) Contaminated single use equipment (ensure proper disposal of, e.g. syringes)

(e) Carcasses (Dispose carcasses as soon as practical, ensure safe disposal—ensure disposed carcasses are not eaten by pest animals)

3. Rules for supply of:

(a) Feed:

(i) Avoid feed contamination by the raw materials used, post-production and during transport, or by exposure to rodents and birds on the property.

(ii) Avoid poor quality or damaged feed, especially once bacteria/moulds are present and can be a concern.

(b) Water:

(i) Avoid surface water contamination, if possible (especially animals on the pasture, outside the “closed water systems”—hard to manage the quality).

(ii) Regularly check water quality and water supply system in the stable/poultry house.

(c) Bedding:

(i) Ensure bedding material is fit-for-purpose.

(ii) Ensure areas where bedding is stored are kept as dry and vermin free as is practically possible.

(d) Equipment

4. Access check (including visitors book/exclusion rules):

(a) Full fencing of the farm surrounding area, and where possible minimise the number of entry points and restrict access to the farm.

(b) Define, and where appropriate signpost, “permitted access areas” for farm contractors (e.g. veterinarians, livestock agents, insemination technicians), delivery and pick-up vehicles (e.g. milk tankers, livestock and feed transporters) and service personnel (e.g. utility company technicians, government officers) and notify relevant operators prior to entry, check also the staff for not keeping animals (e.g. pigs) at backyards/home.

(c) Availability of hygiene lock.

(d) Strict separation of dirty and clean area in hygiene lock.

5. Control of communication with outside influencing factors (building design/structure/effective maintenance—doors, walls, screens, meshes, drain covers and all measures designed to prevent access of animals):

(a) Ventilation, influx of spread agents (e.g. PRRS, Mycoplasma hyopneumoniae)
(b) Control of animal vectors: pest/wild/domestic animals (feral animals; domestic animals, rodents, insects and other invertebrates (such as ticks or mites, rodents, wild birds); e.g. for birds/fly protection install nets

6. Location and environment:
   (a) Pig herds located in an area with high density of pigs (average pig density at municipality level >300 pigs/km²), spotting of wild boars.
   (b) Air: avoid transmission of pathogens via aerosol or dust, whenever possible.

7. Staff education, training, recording, incentives

2.1.2 Internal Biosecurity Subcategories

1. Management of diseases:
   (a) Train facility staff to recognise and report diseased animals:
      (i) Early disease detection systems to be introduced (including new tools of “smart farming technologies”).
      (ii) Frequent visiting (frequency depending on the age/health status of the animals).
      (iii) If detected animal with sign of the disease (either act according the plan or contact veterinarian).
      (iv) Work with a veterinarian to develop treatment protocols and monitor response rates on routine visits to the facility.
   (b) Make available of hospital pens:
      (i) Thoroughly cleaned/disinfected to avoid spread of infection
      (ii) Manage disposing excreta
      (iii) Manage disposing of deadstock animals
   (c) Clean and disinfect all equipment, clothing, boots, etc. that come into contact with ill animals.
   (d) Place a secondary identification on all animals that were treated for illness so they can be rapidly identified and more closely monitored once they have returned to their home pen.

2. Vaccination plan:
   (a) Implement protocols for routine vaccinations.
   (b) Vaccination guns, well cleaned/disinfected/properly changing the needles.

3. Farrowing, suckling period:
   (a) Frequency of cross-fostering of suckling pigs
   (b) Minimise frequency of manipulating (vaccination, castration) suckling pigs

4. Nursery period:
   (a) All-in/all-out-management.
   (b) Avoid mixing of different age groups.
   (c) Minimise stacking and stressful events.

5. Fattening period:
   (a) In pigs, e.g. compartmentalising, working lines, equipment
   (b) Avoid mixing of different age groups.
   (c) Minimise stacking and stressful events.

6. Avoid pets’ movement among sections/stables/poultry houses (pigs, poultry, cattle)

7. Tools and equipment (including, e.g. injectors, dosing automats)

8. Cleaning and disinfection:
   (a) Removal of all mechanic dirties
   (b) Cleaning:
      (i) Mechanic
      (ii) Wet-soap use cleaning
      (iii) Water high pressure washer/high temperature cleaning
      (iv) High importance of proper drying off
   (c) Disinfection
      (Effective against target selected microorganisms, preferably non-toxic/irritating, non-corrosive, non-AMR (co selecting, important to follow thoroughly all phases).
      (i) Application
      (ii) Allowance of contact time
      (iii) Rinse and highly important to let dry again (commercial desiccants, properly cleaned fans and heaters can be used)
   (d) Keep the stable free (the duration depending on consideration of local situation in incidence and type of disease/s in
pervious course of fattening/laying as well as drying of period)
(e) Special attention to water supply/water medication system:
(i) Avoid biofilm formation.
(ii) Avoid residual amounts of antimicrobials.
8. Staff education, training, couching, recording, incentives
(a) Explain and let follow internal biosecurity plan (e.g. once moving across pens/farm facilities by technical staff, keepers, nutritionists, veterinarians etc.)

3 Vaccination

Vaccines have, from the 1930s, made a major contribution to improving farm animal health, welfare and productivity. They are vital components in preventing a wide variety of diseases (RUMA 2016). A survey conducted among citizens in 2016 showed that 66% of respondents believe pets should be vaccinated, while only 54% think the same applies to farm animals. Over 40% of them replied they did not know that animal vaccination prevents the transfer of infectious disease from animals to humans (EPRUMA 2019).

One of the very important tools to improve health status of the herd/flock except following welfare practices and biosecurity is vaccination. The benefits can be seen from different perspectives, e.g. benefit for the individual animal to induce protection and improve its immunostatus, minimising the risk to get sick and reduce mortality (linked also to reduction of secondary, opportunistic infections), help to keep productivity, help build the “herd/flock immunity” and lower transfer of disease. Public health can also be protected through vaccination and a good example of this is the vaccination against zoonotic diseases of livestock animals. Vaccines and proper vaccination strategy at the herd/region level represent the single most cost-effective medical countermeasure that can be used to confront the threat of antimicrobial resistance. The vaccine effectiveness in preventing diseases has been far-reaching, and could significantly reduce the need and use of antibiotics (OIE 2015). Reduced antimicrobial use was also identified as being strongly associated with vaccination, e.g. against Porcine Circovirus type 2 in finishing pig farms (Raith et al. 2016), but vaccinating against more pathogens did not necessarily lead to lower antimicrobial use (Postma et al. 2016). Therefore, it should be borne in mind that vaccines optimally fulfil their potential when used as part of an overall programme of infection prevention and infection control in animal husbandries. Such a programme would be inclusive of veterinary oversight and care, good biosecurity and husbandry practices including welfare rules, proper quality and nutritional and protective balance of the feed, and improved diagnostics (including antimicrobial susceptibility testing, where appropriate) to help ensure pathogen specific, targeted treatment, including, where necessary, treatment by properly chosen antimicrobials (first choice-narrow spectrum whenever possible). The vaccination schedule should be prepared with high level of knowledge of the herd/flock status and anamnesis, considering also parents herds/flocks and should be tailored thoroughly on the exact farm conditions, using both commercial vaccines (in the case that they are appropriate and available), but also thinking on use of autogenous vaccines (if possible to prepare them in high quality standard, and in a way that fit the current pathogens load of the herd/flock).

THINK ABOUT The Research to Support the Development of Multivalent Vaccines

“A reliable supply of pure, safe, potent, and effective vaccines is essential for maintenance of animal health and the successful operation of animal health programmes”

There is the need for research as well as production of safe and effective multivalent vaccines that potentially cover a broad range of issues and disciplines, including

(continued)
discovery of new aetiological agents for inclusion in such vaccines. To close the diagnostic gap, identification of improved surrogate markers of protective immunity is of importance. It should also include an understanding of the mechanisms of interference and diminished efficacy that can be a consequence of combined vaccines. Encouragingly, new technologies and a major shift on how we approach vaccine discovery research may provide new opportunities for addressing these challenges (OIE 2018b).

In July 2019 (SAPHIR 2019), there was released the announcement related to outcomes of the European project under Horizon 2020 umbrella called SAPHIR, that should bring novel vaccine strategies to the market. SAPHIR has selected two representative pathogens of pigs (Porcine Reproductive and Respiratory Syndrome Virus and Mycoplasma hyopneumoniae), chickens (Eimeria spp. and Clostridium perfringens) and cattle (Bovine Respiratory Syncytial Virus and Mycoplasma bovis) to set vaccine development and production approaches applicable to other pathogens.

As many current vaccines fall short of ideal vaccines in one or more respects, promising breakthroughs to overcome these limitations include new biotechnology techniques, new oral vaccine approaches, novel adjuvants, new delivery strategies based on bacterial spores, and live recombinant vectors; they also include new vaccination strategies in ovo, and strategies that simultaneously protect against multiple pathogens. However, translating this research into commercial vaccines that effectively reduce the need for antibiotics will require close collaboration among stakeholders, for instance through public–private partnerships (Hoelzer et al. 2018a, b).

Despite several activities, there exist serious reasons why it is difficult to develop and introduce in practice new (antibacterial) commercial vaccines and those can be summarised as follows:

**Biological:** as, e.g. different serotypes => cross-protection among serotypes is often poor => not sufficiently protect the animal from infection of other serotypes. Also combination of different serotypes limited by interference in the immune response between different strains and tolerability issues due to increased side effects.

**Technical:** as, e.g. investment into manufacturing facilities as a limiting factor

**Economic:** as combinations of serotypes is increasing costs. Also production yields and minimum immunising dose (MID) play a key role for the capacity requirements and cost in commercial manufacturing.

**Regulatory:** as increasing demands on dossiers to be submitted together with application for new, innovative vaccine.

Development of effective and safe vaccines is still a mid- to long-term objective for many bacterial diseases requiring substantial additional “ground” research.

### 3.1 Vaccination Targets and Types of Vaccines

Main target of vaccination in general is to create the immunity that can lead to protection against disease/s. Proper vaccination of animals helps to prevent or even eradicate infectious diseases (animal health target: stop the spread of certain diseases and therefore protect animal health) but also ensures public health (human health target: preventing zoonotic, in contact and food-borne diseases) and especially on farm where previously antibiotic was being highly used, switching to proper health programme together with vaccination can significantly decrease use of antimicrobials.
Ideally herd or flock vaccination is based on the vaccination plan/schedule that is the part of the animal health plan of the certain herd/flock and considers the animal husbandry system. The vaccination plan/schedule should take into consideration a range of different risk factors related to their age, lifestyle, prevailing disease threats and movement of the animals. Specific marker vaccines (DIVA) enable the differentiation between naturally infected and vaccinated animals, what can be of importance in the cross-border movement (export/import) of the animals. These factors should be discussed with the attending veterinarian with knowledge of the herd to decide on the most appropriate choice of vaccine and vaccination plan/protocol. There are three basic objectives in vaccination to provide immunity (RUMA 2016):

- To the animal or group of animals (active immunity)
- To the offspring of an animal via vaccination of the dam (passive immunity)
- To the animal or group of animals and their offspring (active and passive immunity)

Vaccines used can cause active immunisation: vaccine contains either pathogen/s that induce immunity, but not cause the disease, or antigenic components (parts of pathogens). The protective immunity should occur and is based on “immunologic memory”, once faced with the same/very closely similar pathogen heightened immunological response will prevent the disease. Passive immunisation is based on the antibodies, e.g. also maternally derived antibodies transferred either in perinatal period (across the placenta) or post-natal (via suckling the colostrum). Vaccines, whose effect is based on passive immunisation usually contain antibodies (in the form of immune serum or hyperimmune serum, obtained from animals with very high antibody levels to the infection). Typical example is tetanus antitoxin used in farm animals.

The choice of the type of vaccine developed to target a particular organism is based on the nature of the organism itself, its invasive properties and the immune response the organism generates. Consequently, a range of vaccine types are available including modified live vaccines such as attenuated and recombinant vector vaccines and killed/inactivated vaccines, subunit, conjugate and DNA vaccines. Administration of vaccines can be by a wide variety of mucosal delivery routes: oral, nasal, oro-nasal, conjunctival through water, baits, spray, or using the more classical subcutaneous or intramuscular injection to bypass the difficulties of mucosal immune activation (EMA and EFSA 2017) and is detailed per species in Table 2.

Provoking immunological response aiming to gain immunisation/protection against certain

### Table 2  Routes of administration of vaccines in cattle, pigs, poultry and horses

| Cattle | Pigs | Broilers | Horses |
|--------|------|----------|--------|
| Injection (SC/IM) (needle/needle-free) | Injection (SC/IM) (needle/needle-free) | In ovo (hatcheries) | Injection (most common IM, less common SC) (needle/needle-free) |
| Oral (suspension, e.g. lungworm) | Oral (drinking water) | Aerosols (spray, nebulisation, fogging) | Intrasal (in the nostril) |
| Intrasal (anti respiratory diseases) | Intrasal | Oral (drinking water, viral, coccidiosis) | |
| | | Intraocular (Eye drop instillation) | |
| | | Nasal drops | |
| | | Injection (SC/IM; wing web) (needle/needle-free) | |
diseases can be reached by (modified according Jorge and Dellagostin 2017):

- **Live—modified**
  Mostly attenuated vaccines (pathogenic agent is modified/weakened not being able to cause infection, but causing immune response).
  **Pros:** usually requires single dose; usually less likely to produce local reactions
  **Cons:** depending on exact vaccine—troubles if amount of the dose is too small to be correctly administered; slight signs of animal disease can occur; in sick animals at time of vaccination may prevent or reduce the amount of antibody production as well as cause increased expression of the undercurrent disease; not possible administer concomitantly with antimicrobials; interference with maternal immunity in some vaccines; packages should be used immediately after reconstitution (no preservatives, higher risk of contamination); not mixing vaccinated animals to those not vaccinated.

- **Inactivated vaccines**
  Pathogen is killed/inactivated by physical/chemical factors; often need boosters to maintain immunity (the interval indicated for individual vaccines should be followed); proper adjuvant can help to improve protective immune response; mainly producing IgG response, but some also cell-mediated immunity.
  **Pros:** vaccine cannot cause disease; no general illness if healthy animals vaccinated; less likely influenced by maternal immunity (some vaccines can); longer shelf life; less prone to contamination, if preservatives used.
  **Cons:** higher volumes than in live vaccines to be administered (especially older vaccines); the quantity of the immune response is mainly, but not always, dependent on the amount of antigen present in the vaccine; due to adjuvants local reactions could appear (some persisting for long time); twice or more administration—risk of improper compliance; increase stress from animals handling; in killed, whole bacteria containing vaccines, higher risk of induction of autoimmunity troubles via molecular mimicry.

- **Recombinant subunit**
  Pathogen-specific genetic material is processed using genetic engineering technology to produce immunity stimulating proteins, primarily humoral immune response, need of adjuvant.
  Live recombinant vaccines: still able to multiply in cells, usually give an excellent immune response (via simulating natural infection). Disease virulence genes can be altered/removed, thereby safer vaccines can be produced; also genes allowing spread to environment can be removed.

- **Purified protein/subunit vaccines**
  Made up of either monoclonal antibodies or protein molecules (purified antigens) that have been extracted from pathogens or the exotoxins they produce.

- **RNA/DNA based**
  Humoral and cellular immune responses. Challenges in adequate cellular uptake and expression.
  Long-term persistence of immunogen. The risk of integration of nucleic acid or part of it into host genome cannot be completely excluded. Unstable and quite expensive production (for RNA vaccines).

- **Non-vaccine immunomodulators**
  Alter the immune response by augmenting or reducing the ability of the immune system to produce antibodies or sensitised cells that recognise and react with the antigen which initiated their production. The mode of action includes augmentation of the anti-infectious immunity by the cells of the immune system including lymphocyte subsets, macrophages and natural killer cells. Other mechanisms can involve induction or restoration of immune effector functions. Use of immunomodulatory agents seems an attractive approach as an adjunct modality for control of several parasitic diseases. Examples are cytokines, interferons, interleukins and tumour necrosis factors (Ratna and Arora 2018).

- **Combination vaccines**
  An issue of the multistrain/multisertype as well as combined bacterial/viral infections exists. Those cases are the most
complicated to be prevented by vaccination programmes. For some purposes they fit the combination vaccines, that differ from those “single disease/pathogen” vaccines that provide specific protection for one organism or strain of an organism.

Combination vaccines:

- May present antigens that include different strains of the organism and/or provide protection against a number of microorganisms often of the same type such as in the clostridial vaccines.
- May be designed against different microorganisms which result in the same types of disease (e.g. respiratory disease of calves) and may combine several viral antigens and also in some cases bacterial components.
- May contain completely different antigens (in terms of diseases caused) but they are administered together as they are important causes of infection in the species concerned or they provide required enhanced protection at certain stages in the animal’s life such as with sheep (vaccines against clostridial diseases/pasteurellosis).
- Require proper design and formulation to ensure that they are produced so that each component is in sufficient quantity to initiate an immune response in the animal.
- Can pose an advantage of reduced number of vaccination, decreasing risk from potential stress from handling and the administration of the vaccine.
- Can pose another advantage—for the farmer is less demanding to remember as to when to undertake initial vaccination or subsequent boosters.

3.2 Routes of Administration of Vaccines, Main Reasons for Vaccination Failure

For different types of vaccines, different species and different production categories/ husbandry systems specific routes of administration are available for the respective veterinary medicinal products. Table 2 gives a brief summarisation of them, showing also that vaccination can be strictly individualised (horses via administration by injection/intranasally) or is available/applicable for groups of animals or even flocks/herds.

In the cases of individualised administration the risks of incorrect dose are minimal as well as no risk, that certain animals will not receive the vaccination. On the other hand, the mass vaccination (e.g. via vaccines administered orally via drinking water) is considered to pose some advantages as improved safety and compliance, and easier manufacturing and administration as well as stimulation of humoral and cellular immune responses at both systemic and mucosal sites to establish broader and long-lasting protection. On the other hand, difficulties especially due to possible damage of the vaccine active parts by gastrointestinal tract conditions and finally delivery of sufficient amount of antigen to provoke adequate immunogenic response cannot be forgotten. Therefore, oral vaccines are required to be designed for successful delivery of the intact and active antigen to the intestine, proper transport across the mucosal barrier and subsequent sufficient activation of antigen-presenting cells. Care should be paid to the proper use and administration of such vaccines to achieve the effect expected.

Essential factors that must be taken into account when using a vaccine consist of proper handling with vaccine, correct administration and use, performed by well-trained staff that follows the approved product texts being aware of the use instructions (route of administration, correct site of administration of injectables) as well as warnings, recording of vaccination is important not only if some troubles occur, but, e.g. having an evidence for the future herd health/vaccination plan(s).

Possible failures (as listed in Table 3) can be influenced by several factors, but some of mistakes can be relatively easily avoided (incorrect handling/use), some need the effort, but could be overcomed (vaccination programme weaknesses, improper quality/suitability of
| Due to incorrect handling | Due to incorrect use | Weakness of vaccination programme | Vaccine-related issues | Animal related |
|--------------------------|---------------------|----------------------------------|-----------------------|---------------|
| Incorrect storage (cold chain issues, not exposing sunlight) | Incorrect dose | Unavailability of vaccine (permanent, in the period of need) | Low potency | Poor health/unwell/stressed animals |
| Incorrect handling not warmed enough prior to administration (troubles to pass needle, temperature shock in small animals) | Incorrect route of administration | Incorrect timing | Manufacturing quality problems (inter-batches differences, poor batch quality) | Immunological interference (e.g. maternal immunity) |
| Using improper syringes/devices (especially in oily suspensions) | Failure in proper administration (e.g. broken needle, due to improper needle size/not sufficiently sharp; SC/IM failures) | Suboptimal schedules (number of doses, intervals among doses) | Serotype not covering the field isolate | Production/age status |
| Improper cleaning/disinfection/not letting to dry off (especially live vaccines susceptible to the rest of disinfecting agents) – water supply systems – if use automatic syringes | No booster vaccination | Misdiagnosis of disease leading to incorrect vaccination scheme | | Young: Immature immune system |
| | Vaccination of unwell animals (mainly risk of adverse vaccine effect) | Interference with other vaccines | | Mother close to birth: less immune responsive |
| Partly used bottles—risks of contamination (especially when not aseptically collected from vial/bottle) | Vaccination under concomitant antimicrobial use in live vaccines (Lawsonia vaccines in pigs) | Interference with other vaccines | | Suboptimal immune response |
| Partly used bottles, damage of the stopper—oxidation damage of the antigen or carrier | Mixing vaccines in one syringe, once not recommended | | | Infection already in incubation period (e.g. viral infections/mycoplasma infection suppressing immunity response) |
| Partly used bottles—temperature fluctuation leading to damages, especially in live vaccines longer duration of reconstitution causes death of the vaccination microorganism | Injection into same injection site (even in several days) if warned not to do so | | | Nutrition/feel deficiencies—e.g. especially proteins, vitamin A and E, selenium. |
| Vaccine beyond the expiry date | | | Not all animals obtained their dose (e.g. oral vaccines via drinking water) | |
vaccines), some are animal related and the influencing is hard/need big experience of vet.

3.3 Diseases for Which Vaccines Could Reduce Antimicrobial Use in Animals

Principally, based on consideration of the following factors OIE made the prioritisation of the diseases, for which vaccination can reduce need for use of antimicrobials (OIE 2015, 2018a, b):

- Identification of the most prevalent and important bacterial infections
- Identification of common nonbacterial infections (e.g. protozoal, viral) showing clinical signs that trigger empirical antibiotic treatment (e.g. for diarrhoea) and which also result frequently in bacterial co-infection or secondary bacterial infection that need use of antimicrobials
- An assessment of antibiotic use in response to the syndromic indication or diagnosed disease
- The availability of a vaccine(s), and if available, their effectiveness
- The potential for a new or improved vaccine to reduce the need for antibiotic treatment

Proposed lists are for chicken, swine (according diseases/pathogens) and fish (according groups of fish species/pathogens) diseases (OIE 2015), continuing with lists for cattle, sheep and goats (OIE 2018a). Below text also contains other (bacterial diseases) of poultry, pigs and cattle that were not prioritised by OIE, but are also treated or prevented by use of antimicrobials and therefore, vaccination can bring an achievement of better health status as well as minimise use of antimicrobials (at least in the region of Europe). There are also examples of vaccines whose use has led to significant and well-described decline in the use of antimicrobials in different parts of the world and in different types of animal species/types of husbandries. This is the case of the vaccination against furunculosis in fish (salmon) in Norway, followed by the huge decrease use ATM in aquacultures (Midtlyng et al. 2011). In Denmark vaccination against Lawsonia intracellularis, causative agent of ileitis in pigs, also helps to decrease the use of certain group of antimicrobials (DANMAP 2014).

3.3.1 Poultry Diseases

Two main bacterial pathogens of Gallus gallus (considering broilers, breeders and layers) were identified:

- *Escherichia coli*
  Key diseases to be covered were identified: yolk sac infection (omphalitis), airsacculitis, cellulitis, salpingitis and peritonitis. There were also recognised limitations of the use of vaccines as degree of strain coverage (fully cross-protective), ease of administration (e.g. aerosol), minimal adverse effects. Among other challenges were that vaccine is needed for very early stages (consider possibility to stimulate at maternal level). Within the EU area both live and inactivated vaccines (monovalent or polyvalent) are available, and there is also possibility to detect the *E. coli* strains and profiles and use autogenous vaccines.

- *Clostridium perfringens* (type A)
  Causing necrotic enteritis and high production losts. Therefore, broadly prevented by antimicrobials. The duration of passive immunity induced by toxoid vaccines in layers is short lasting. The need for a vaccine to achieve active immunity, particularly for broilers.

Further examples of bacterial pathogens causing the diseases in Gallus including those for which antimicrobials are also frequently used and for which vaccines are available in the territory of Europe are as follows (live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation are available):

- *Salmonella* spp. (mostly against *enteritidis, typhimurium, gallinarum*)
- *Pasteurella multocida*
- *Ornithobacterium rhinotracheale*
- *Mycoplasma* (gallisepticum, synoviae)
Also coccidial infection predisposes to secondary bacterial infections and improvement in the degree of cross-protection of current vaccines would result in a decrease of secondary bacterial infection. Live vaccines for passive and active immunisation are available in the European territory.

Two key viral infections influencing health and immune status of animals and getting them prone for other bacterial diseases, for which vaccination is available, are Infectious Bursal Disease Virus (IBDV) and Infectious Bronchitis virus.

Those reading this chapter can ask for the information related to vaccination of other bacterial diseases of poultry with increasing importance not only from the perspective of animal health, but having also potential to affect human health (e.g. staphylococcal and enterococcal infections). It should be unfortunately noted that up to this day, despite some attempts, as e.g. study on vaccination of breeder hens with a polyvalent killed vaccine for pathogenic Enterococcus cecorum, that shows that does not protect offspring from enterococcal spondylitis (Borst et al. 2019), there is no available commercial vaccine against Staphylococcus spp. and Enterococcus spp. in poultry.

3.3.2 Swine Diseases

Nine bacterial pathogens and three viral infections (resulting frequently in secondary bacterial infections) were identified by OIE to be considered when setting the priority list. The main issue of currently existing vaccines are the range of pathogen strain coverage and degrees of cross-protection.

**Respiratory Tract Infections of Swine Main Causative Agents and the Vaccination Possibilities**

- **Pasteurella multocida**
  Associated with pneumonia, an effective toxoid vaccine for atrophic rhinitis exists. Portfolio of live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation is available within the European territory, autogenous vaccines use also possible.

- **Streptococcus suis**
  Causing infections as meningitis, arthritis, sepsis or infection of soft tissues mainly in post-weaned piglets. In addition to the current most worldwide spread sequence type 2 vaccine will be beneficial to have vaccines protected against other strains (e.g. sequence types ST1, ST 20 described for the EU region and the other STs for other world regions). Due to this variability is hard to find “universal vaccine”. Improvement of immunogenicity is needed and maternal antibody interference with the H. parasuis vaccine should be solved. Also more studies on maternal antibody interference are necessary in order to determine conclusively whether it is preferable to vaccinate sows or piglets, and when exactly. Actually, autogenous bacterins are discussed as the available option in the field, keeping in mind that improved diagnostic and proper understanding the epidemiology of S. suis diseases is essential for using bacterins successfully (Rieckmann et al. 2020). These vaccines are bacterins prepared for a specific farm (need for bacteriological analysis of samples from affected farm). As such, despite the huge variation in S. suis infections by region, vaccinated animals are protected from the same strain (s) causing clinical problems within the herd in question.

- **Actinobacillus pleuropneumoniae**
  Causing pleuropneumonia in pigs, live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation are available. Types of vaccines currently available are bacterins based (washed and killed whole bacteria with serotype-specific protection), mainly autogenous vaccines, with diagnosed and isolated serotype/s from exact farm and purified toxoid-based vaccines (sometimes enriched with surface proteins): mostly Apx I, Apx II and Apx III toxoids are present. There is a strong interference with maternal antibodies: usually, first dose should not be applied before 7–8 weeks of age. Also not sufficient single dose-booster dose needed. Interestingly, also high level of antibodies after infection or vaccination do not eliminate
APP from tonsils of carriers. It is beneficial to use, e.g. new serotyping PCRs (mPCR1 and mPCR2) as tools to identify virulent serotypes for choosing the proper vaccination (by commercial or autogenous vaccine)—one of the most effective (but not routinely available yet) is the whole genome sequencing, that allows also to recognise new serotypes (Bossé et al. 2018).

- **Mycoplasma hyopneumoniae**
  Pathogen with an important role in the porcine respiratory disease complex. The vaccine does not eradicate the pathogen. Live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation are available in the European territory. Vaccination schemes frequently used in the European region are traditional two-shot formulations, one-shot formulations, and bivalent one-shot formulations containing both *M. hyopneumoniae* and porcine circovirus type 2 (PCV2) antigens. In general, vaccination reduces the occurrence of clinical signs and lung lesions and improves performance, but on the other hand does not prevent colonisation of the respiratory tract epithelia by mycoplasma organisms (Cvjetković et al. 2018).

Further examples of bacterial respiratory pathogens causing the diseases of pigs including those for which antimicrobials are also frequently used and for which vaccines are available in the territory of Europe are as follows (live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation are available):

- **Haemophilus parasuis**
- **Pasteurella multocida**
- **Bordetella bronchiseptica**

Two key viral infections influencing respiratory tract polyfactorial infections spread, including secondary bacterial infections, for which vaccination is available and could help minimising of use of antimicrobials are:

- Porcine Reproductive and Respiratory Syndrome (PRRS) virus
- Swine Influenza virus (SIV)

**Enteric Tract Infections in Swine Main Causative Agents and the Vaccination Possibilities**

- **E. coli**
  One of the most important pathogen causing enteritis as well as oedema disease, for which maternal vaccines which provide passive immunity to neonates exist. Despite this for *E. coli* vaccines in weaners/finishers, complications are maternal antibody interference and the relatively short window for induction of immunity. Some new vaccines exist, e.g. live non-pathogenic *Escherichia coli* O141:K94 (F18ac) and O8:K87 (F4ac), as well as combined vaccine for F4 and F18, but further research is needed. Live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation are available as well as use of autogenous vaccines.

- **Lawsonia intracellularis**
  Porcine proliferative ileitis is a major economic burden for the swine industry, affecting growing pigs and young adult pigs. A modified live-attenuated vaccine has been commercially available since 2001, but due to the live nature of the oral vaccine, concurrent use with antibiotics effective against *L. intracellularis* was not possible. Recently (2018) inactivated injectable vaccine has been introduced, that is intended to be administered to 3-week-old pigs under typical field conditions that can pose protection against ileitis, help reduce bacterial shedding 15-fold and help maintain gut barrier function integrity (Roerink et al. 2018).

- **Brachyspira hyodysenteriae** and **Brachyspira pilosicoli**
  Are considered to be re-emerging issue, not solved by change of husbandry practices, but in most cases sold by repopulation and restructuring of the husbandries. As for vaccine, the issue is not easy culturing and work with strains to develop vaccine. No
commercial vaccines are available for prevention of *B. pilosicoli* infections. In pigs studies with autogenous bacterin induced systemic antibody titres, but the vaccinated animals still became colonised and developed diarrhoea (Hampson 2018). Recently, recombinant Bmp72 C-terminus has been shown to give potential to be developed for use as a vaccine component to provide protection against *B. pilosicoli* infections (La et al. 2019b). Currently (2019), an atypical weakly haemolytic strain of *Brachyspira hyodysenteriae* has been described to occur in Europe and Australia, and due to its avirulence it can be used to protect pigs from developing swine dysentery (La et al. 2019a).

Further examples of bacterial enteric pathogens causing the diseases of pigs including those for which antimicrobials are also frequently used and for which vaccines are available in the territory of Europe which are as follows (live and inactivated vaccines (monovalent or polyvalent) for active or passive immunisation are available):

- *Clostridium perfringens*
- *Salmonella* spp.

As for rotavirus infections, influencing the whole pig performance and can be complicated by bacterial enteric pathogens entry, authorised vaccines are available protecting against these infections.

Further vaccination to be considered in pigs are:

- *Erysipelothrix rhusiopathiae*
- PCV2 (viral)

Intestinal infections are a major problem and account for a large proportion of total antimicrobial consumption in Danish pigs. Viral infections—such as swine influenza, PRRS and porcine circovirus type 2 (PCV2)—also increase antimicrobial consumption as they are associated with secondary bacterial infections. Given that many of these diseases can be handled with vaccinations and good management, further reduction in antimicrobial use is possible without compromising animal welfare. The sales of vaccines for pigs increased, according to the figures provide by the Danish Veterinary and Food Administration from 28 million doses in 2009 to 55 million doses in 2017 (FAO 2019).

### 3.3.3 Cattle Diseases

In cattle, considering young animals (new born calves in which antimicrobials are used in milk replacers) as well as dairy and feedlot cattle use of antimicrobials is of concern. Considering different systems (respiratory, gastrointestinal, urogenitary) as well as specific disease complexes (mastitis, lameness) there were identified diseases caused either primarily by bacterial pathogens (or viral agents with concomitant or secondary bacterial pathogens contributions) that can be prevented by proper vaccination. Both OIE priority lists (OIE 2018a, b) as well as vaccines and other immunological/biological veterinary medicinal products available predominantly in the European region were taken into account where following text was completed.

**Respiratory Tract Infections of Cattle Main Causative Agents and the Vaccination Possibilities**

The bovine respiratory disease complex (BRD) is a multifactorial disease attracting high levels of antimicrobial use in cattle, especially in feedlots. For vaccine development, a syndromic, multi-pathogen, approach would be preferable to address all animal health risks (OIE 2018a, b).

The major organisms involved are:

- *Mannheimia haemolytica* (MH)
  Regarded as a primary pathogen and features a lack of cross-protection among different strains. Most vaccines are targeted MH serotype 1, also in combination with HS, or with viral inactivated parts (bovine respiratory syncytial virus), parainfluenza 3 virus and/or bovine viral diarrhoea virus.
- **Pasteurella multocida (PM)**
  Primary and a secondary pathogen causing respiratory diseases. It was recognised that the existing vaccines notably have marginal efficacy and there is a potential lack of cross-protection among PM field isolates (where autogenous vaccines can be of choice).

- **Histophilus somni (HS)**
  Opportunistic pathogen, that is less common, in the EU region commercial vaccines available (including e.g. combined vaccine against HS and MH used in calves from 2 months of age, two doses).

- **Mycoplasma bovis**
  The role in BRD is considered to be lower than for other pathogens, and that although it was found with increasingly higher occurrence, its role as a causal agent in BRD was uncertain.

Combined vaccines for bacterial and viral diseases as well as individual agents covering vaccines are available at least in the European region:

- **Bovine viral diarrhoea virus (BVDV):** Considered by the group to be the viral pathogen that elicits the most significant use of antimicrobial agents in BRD.
- **Parainfluenza virus 3 (PI3), BHV-1 (IBR):** Both these viruses were recognised as being lesser contributors to antimicrobial use, and existing vaccines are effective and safe. For IBR, DIVA vaccines have been shown to be useful for eradicating the disease in several countries of Europe.
- **Bovine respiratory syncytial virus (BRSV):** Adequate vaccines are available.
- **Bovine coronavirus:** Recognised as an emerging respiratory pathogen. While a vaccine is available, its efficacy is uncertain.

Apart from BRD, the group considered another respiratory disease as within the scope, Contagious Bovine Pleuropneumonia (CBPP, *Mycoplasma mycoides* subsp. *mycoides*). CBPP is one of the most relevant diseases in Africa, where it entails high use of antimicrobial agents, which could lead to establishment of a carrier state.

**Enteric Tract Infections in Cattle Main Causative Agents and the Vaccination Possibilities**

Enteric diseases are an important cause of antimicrobial use, especially in feedlot systems:

- **Fusobacterium necrophorum**
  Entails high use of antimicrobials, especially in feedlots, arising from acidosis. No vaccines are labelled for enteric disease/acidosis/liver abscesses; and off-label use of *F. necrophorum* vaccines designed for other diseases provides limited efficacy.

- **Enterotoxigenic E. coli**
  Provokes a high use of antimicrobials, especially in dairy farms. Effective vaccines do exist, in the European region several vaccines are available as, e.g.:
  - Combined vaccines declaring reduction of severity of diarrhoea caused by *E. coli* F5 (K99), of incidence of scours caused by rotavirus and shedding of virus by calves infected with rotavirus or coronavirus
  - Combined vaccine stimulating serological and Colostral antibodies against rotavirus and coronavirus antigens and against *E. coli* K99, Y, 31A and F41 antigens passed to the calf to reduce neonatal diarrhoea infection caused by agents containing these antigens (target categories pregnant cows and heifers, two doses, second at least 2 weeks prior calving)

- **Salmonella enterica**
  Is a notable zoonotic disease. Strains many times have different and sometimes broad portfolio of genes conferring antimicrobial resistance. The disease’s greatest effects on animals are in dairy calves soon after birth, which are exposed to the challenge before the onset of immunity that might be derived from vaccination. *Salmonella* spp. vaccines are available to address the prevalent subspecies/serotypes in the various regions (e.g. *S. enterica* serotype Dublin, *S. enterica* serotype Dublin)
serotype Newport, *S. enterica* serotype Typhimurium). These vaccines are generally used in herd programmes to control the level of *Salmonella* spp. bioburden within the vaccinated herd, leading to lower levels of *Salmonella* spp. exposure to the new animals entering in the herd. This then results in a lower level of the disease.

- **Mycobacterium avium** subsp. *paratuberculosis*
  Causing Johne’s disease, often undiagnosed or misdiagnosed, and maybe mistaken for other forms of bacterial enteritis. Vaccine availability is geographically limited, and existing products present several drawbacks.

- Bovine rotavirus and bovine coronavirus are also causal agents of neonatal diarrhoea in calves, which may be treated with antimicrobials because the cause of symptoms is frequently undifferentiated. Rotavirus infections, being more prevalent than coronavirus, are likely to attract higher use of antimicrobials. In both cases, effective vaccines exist, several of them as combined vaccines (together with selected types of *E. coli*)

- **Cryptosporidium parvum** and *Eimeria* spp. no vaccines available for cattle.

- As there was indicated overuse of anthelmintic also provoking anthelmintic resistance, therefore need for vaccines against Helminths research and development is high.

Non-vaccine immunological veterinary medicinal products like bovine concentrated lactoserum also should not be forgotten, that is intended to be used for neonatal calves less than 12 hours of age and which contains high levels of IgG against *E. coli* K99 (indicated to be used for the reduction of mortality caused by enterotoxicosis associated with *E. coli* F5 (K99) in the first days of new born calves).

**Mastitis Main Causative Agents and the Vaccination Possibilities**

- *Streptococcus agalactiae*, *Streptococcus uberis*, Coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Escherichia coli* and *Mycoplasma bovis*.

- Antimicrobial use for mastitis is considered to be higher in modern, intensive dairy production located in stables rather than in grass-based production. The occurrence of multiple strains, the lack of cross-protection of available vaccines, and the difficulty of building a specific immune response at the site of infection were identified as current difficulties. Other (less frequent and less demanding antimicrobial use) mastitis causative pathogens are not discussed. Dry cow therapies provide control against a number of different contagious and environmental pathogens. From a herd perspective, development of a vaccine against individual pathogens will not eliminate the need for control of the other pathogens often found in infected cows. Development of combination vaccines that address the common mastitis pathogens would offset this issue, but represents a difficult technical challenge that would require a significant investment in research and development (OIE 2018a, b).

- Combined vaccine declaring reduction of the incidence of subclinical mastitis and the incidence and the severity of the clinical signs of clinical mastitis caused by *Staphylococcus aureus*, coliforms and coagulase-negative staphylococci exist at least in EU region, three injections needed.

- Recently (2018) was also granted the marketing authorisation to another one veterinary medicinal product containing the active substance called biofilm adhesion component including lipoteichoic acid, which is derived from the sticky film produced by *Streptococcus uberis* strain 5616. The product is indicated for an active immunisation of healthy cows and heifers to reduce the incidence of clinical intramammary infections caused by *Streptococcus uberis*, to reduce the somatic cell count in *Streptococcus uberis* positive quarter milk samples.

- Biological, non-vaccine veterinary medicinal product authorised in 2015 in European Union is also further taken into account as solution for injection intended to be used in
dairy cattle and heifers. As for composition, ovine granulocyte colony stimulating factor (bG-CSF) is a modified form of the naturally occurring immunoregulatory cytokine, which is a naturally occurring protein produced by mononuclear leukocytes, endothelial cells and fibroblasts. The immunoregulatory activities of granulocyte colony stimulating factor concerns notably cells of the neutrophilic granulocyte lineage which bear cell surface receptors for the protein. The use of bG-CSF increases the number of circulating neutrophils and enhances myeloperoxidase hydrogen peroxide halide mediated microbiocidal capabilities of neutrophils. Direct or indirect influence on other cells/receptors and cytokine pathways are also predicted.

Cattle Lameness Main Causative Agents and the Vaccination Possibilities

Lameness is a priority issue for the dairy sector, together with mastitis. Interdigital and digital dermatitis as the dominant lameness syndromes attracting antimicrobial use were identified by OIE (2018a, b):

- **Fusobacterium necrophorum**
  Considered as a major pathogen of importance, but in the EU region also *Bacteroides melaninogenicus, Dichelobacter nodosus, Porphyromonas levii, Prevotella melaninogenica, Treponema spp. and Trueperella pyogenes* are of concern (Kontturi et al. 2019). For this kind of disease is frequently used also one of the critically important cephalosporin of third generation (strong selector of ESBLs)—ceftiofur. Veterinary medicinal products containing ceftiofur are many times preferred to older molecules due to zero milk withdrawal period in dairy cattle, what promote further use of ceftiofur by vets and farmers.
  Vaccines are not available.

- **Pasteurella multocida** as a causative agent of haemorrhagic septicaemia, provokes high use of antimicrobials, even though the existing vaccines appear effective.
- **Leptospira spp.**
  Regional differences in serovars act to limited vaccine availability and use, but combined vaccines (e.g. against six serotypes together currently authorised).
- **Bacillus anthracis**
  Effective vaccines are available.
- **Clostridium spp.**
  Mostly autovaccines: *Clostridium perfringens* (A, B, D), but also for other Clostridia (*C. difficile, C. novyi, C. sordellii* etc.).

Genitourinary Tract Infections in Cattle Main Causative Agents and the Vaccination Possibilities

Metritis/endometritis syndrome associated with *Trueperella pyogenes, E. coli* and *Fusobacterium necrophorum* was considered by OIE experts. No vaccines authorised to cover these metritis pathogens.

3.4 Veterinary Autogenous Vaccines

Another possibility of reducing the need for use of antimicrobials also in the cases where no commercial vaccine is available, or where commercial vaccine covering certain bacterial/viral specific serotypes or combination of both is not accessible, veterinary autogenous vaccines can be the functioning option. One example can be from pig farming, where autogenous vaccination of the sows with a vaccine based on exhB-positive *Staphylococcus hyicus* isolates reduced metaphylactic treatment with antimicrobials as well as the morbidity and mortality rates in weaned pigs compared with pigs from non-vaccinated sow batches (Arsenakis et al. 2018).

Autogenous vaccines can provide an individual solution where licensed commercial vaccines are not available or lack effectiveness due to the antigenic diversity of the causal, bacterial and
viral, agent. In certain situations of clinical practice, therefore, they represent a unique option for use in addition to commercial vaccines. Examples of autogenous vaccines used in the European region are listed in the Table 4. As veterinary autogenous vaccines are considered inactivated vaccines which are manufactured using a disease agent isolated in a particular epidemiological unit (herd/flock) and are intended and permitted for use only in that unit. This means that a farm may include more than one herd/flock, provided the flows of animals are clear and clearly documented. The new Regulation on Veterinary medicinal products speaking about the veterinary autogenous vaccine indirectly by characterising them under the Scope (Article 2, paragraph 3) as inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link. Animal keepers and owners

| Table 4 | Examples of the bacteria used in VAV (Hoelzer et al. 2018b, amended) |
|---------|-------------------------------------------------|
| Species/genus of bacteria | Virus |
| **Pigs** | |
| Respiratory | Actinobacillus pleuropneumoniae |
| | Histophilus somni |
| | Mannheimia haemolytica |
| | Mycoplasma hyorhinis |
| | Pasteurella multocida |
| | Staphylococcus pk-negative |
| | Staphylococcus hyicus |
| | Staphylococcus aureus |
| | Streptococcus dysgalactiae |
| | Streptococcus equisimilis |
| | Streptococcus hyosynoviae |
| | Streptococcus suis |
| | Trueperella pyogenes |
| Gastrointestinal | Rotavirus |
| Other | Porcine rotavirus A |
| | Corona virus |
| | Clostridium difficile |
| | Clostridium novyi |
| | Clostridium perfringens |
| | Clostridium perfringens A |
| | Clostridium perfringens D |
| | Escherichia coli |
| | Haemophilus parasuis |
| | Streptococcus suis |

| **Cattle** | |
| Respiratory | Histophilus somni |
| | Clostridium perfringens |
| | Moraxella catarrhalis |
| | Mannheimia haemolytica |
| | Pasteurella multocida |
| | Trueperella pyogenes |
| Gastrointestinal | Clostridium perfringens |
| | Clostridium perfringens A |
| | Clostridium perfringens D |
| | Clostridium perfringens B |
| | Escherichia coli |

| Mastitis | Klebsiella pneumoniae |
| | Staphylococcus aureus |
| | Streptococcus suis |
| Keratoconjunctivitis | Moraxella bovoculi |

| **Poultry** | |
| Bacterial | Avibacterium |
| | Bordetella avium |
| | Bordetella bronchiseptica |
| | Clostridium perfringens |
| | Enterococcus cecorum |
| | Enterococcus faecalis |
| | Enterococcus spp. |
| | Escherichia coli |
| | Gallibacterium anatis |
| | Mycoplasma spp. |
| | Ornithobacterium rhinotracheale |
| | Pasteurella multocida |
| | Riemerella anatipestifer |
| | Staphylococcus aureus |
| Viral | Adenovirus |
| | Infectious bronchitis virus |
| | Reovirus |
| | Rotavirus |
of food-producing animals must keep record of the use of autogenous vaccines.

Active substance (antigen) of the product are inactivated immunogens of the relevant isolates, which activate protective mechanisms (macrophages, opsonins, B and T lymphocytes) and this leads to establishment of the immunity against individual causative agents. The individual components of the vaccine are in the organism gradually degraded and processed by the immune system. This leads to creation of specific antibodies against individual components.

Generally speaking, veterinary autogenous vaccines can be produced for any species of animal. The disease agents isolated from the herd/flock are cultured, identified, thoroughly typed (e.g. serotypes and virulence factors) and selected depending on their virulence factor content and/or immunogenicity traits. Selected pure cultures of the isolates are propagated. Then following several processing steps finally living compartments (bacterial cells/viral particles) are thoroughly inactivated, antigens gained by specific processes are purified and concentrated. The active ingredient of the each specific veterinary autogenous vaccine can represent several compartments as, e.g. toxoids APX I, II and III, outer membrane proteins and lipopolysaccharides of inactivated bacterium of different serotypes (e.g. *Actinobacillus pleuropneumoniae* of serotypes 2 and 9). There is, like in commercial vaccines, also important role of selection of adjuvants, to stimulate immune answer.

The period of use of single veterinary autogenous vaccine is limited, but repeated production of VAV on the basis of disease agents isolated from the herd/flock epidemiologically linked to farm of origin of the “first” isolate is possible. Several companies on the EU market is able to perform all steps of production of the veterinary autogenous vaccines under GMP-compliant conditions.

Because autogenous vaccines take some considerable time to produce they are only useful in case of chronic or recurrent disease/s. In practical conditions several weeks (4–6 weeks for bacterial and in the case of combined viral/bacterial vaccines or e.g. combination of serotypes 6–8 weeks) are usually necessary to produce the vaccine.

Despite the advantages (as e.g. improved efficacy targeted on exact serotypes of pathogens), there are also disadvantages as such as the fact that each vaccine carries the risk of unwanted or adverse effects as autogenous vaccines are not subject of full battery of tests as commercially produced vaccines that are more broadly tested.

### 3.5 Conclusion to Vaccines

Vaccines have contributed significantly to the control of infectious diseases in production animals, and both commercial as well as autogenous vaccines tailored for epidemiological units can also help to reduce the need for especially prophylactic use of antimicrobials. Despite the use of vaccination, certain infectious diseases still wait for solution. In individual herds other alternative tools may have a more significant effect. Also it should be noted that vaccines against viral diseases can impact through prevention of immune suppression and secondary bacterial infections prevention the overuse of antimicrobials. It should be also highlighted that despite significant technical progress, there is a big challenge for development of the new generation vaccines/or more generally speaking immunologicals, with improved design, ease of administration as well as efficacy. For the cases where commercial vaccines are not an option autogenous vaccines can be a potent tool, but further harmonisation of their manufacturing and conditions in the EU region will be beneficial.

As indicated already in RONAFA report (EMA and EFSA 2017) and later on SAPHIR (2019) revisited, there are main areas where antimicrobials are used and can be solved by vaccination:

- For pigs: post-weaning diarrhoea causative agents, vaccines against Porcine Reproductive and Respiratory Syndrome Virus, *Mycoplasma hyopneumoniae* and *Streptococcus suis* are needed.
• For poultry: vaccines against various types of *E. coli* as well as against coccidia (*Eimeria* spp.) and *Clostridium perfringens*.

• For cattle: mastitis and viral diseases in veal production, but new (or re-emerging) pathogens such as bovine Respiratory Syncytial Virus and *Mycoplasma bovis* are of concern.

**THINK ABOUT** Mycotoxins and effectivity of vaccination and influence on susceptibility to pathogens causing infectious diseases

There is no question that mycotoxins have an effect on the immune system, but exact mode of such (inter)action continues to be discussed. Numerous studies supporting the fact that mycotoxins have an effect on the efficiency of the immune response— aflatoxins, ochratoxin A, fumonisins, zearalenone, trichothecenes, deoxynivalenol and T-2 toxin belong among mycotoxins that all target the immune system, but have also further toxic effects (Pierron et al. 2016). It is well recognised that in poor quality feed containing moulds or directly mycotoxins produced by them harm the health and immunity of the animals. Aflatoxins interact with the cytokines, a part of the immune system. They also influence the important inflammatory response. In pigs vaccinated with model antigen, an impaired lymphocyte activation in pigs exposed to Aflatoxin B1 was suggested as one of the outcomes (Meissonnier et al. 2008). Ochratoxin A also effects the efficacy of vaccinations. In weaned pigs ingested diet contaminated by ochratoxin A was proved decreased capacity to respond with cytokine expression (mRNA and protein) to ex vivo challenge with lipopolysaccharides (LPS) (Bernardini et al. 2014). Therefore, it is very important to consider quality of feed and possible mycotoxin contamination of it when developing herd management programmes, to ensure maximum efficacy of vaccinations. Influence of *Fusarium* mycotoxins on susceptibility to infectious diseases in pigs via affecting the intestinal health and the innate as well as adaptive immune system has also been described (Antonissen et al. 2014).

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**4 Other Tools Available to Keep Animals Healthy**

**4.1 Disease Management Strategies**

The eradication of a clinically relevant or production-limiting disease can, in well-defined cases/criteria can also help to reduce the use of antimicrobials and bring economic benefits (Sasaki et al. 2015). Those criteria consist of:

- Life cycle and transmission dynamics precise information
- Accessible and robust diagnostic tools (satisfactory sensitivity and specificity)
- Availability of the effective, efficient and practical interventions (e.g. a vaccine) to interrupt the transmission pathways of the agent

Most effective are interventions, where there is only one maintenance host and when the disease cannot/have very limited amplification in the environmental conditions.

Except biological, scientific, technical conditions, also societal and political commitment to perform measures are of critical importance for disease eradication (EMA and EFSA 2017). The use of vaccination programmes or antimicrobial treatment before the introduction of an eradication campaign can help reduce the susceptible population (Dieste-Perez et al. 2016) and so-called marker vaccines, together with a companion Differentiating Infected from Vaccinated Animals (DIVA) test can be particularly supportive.
Certain fundamental principles need to be fulfilled in the preparatory stages and prior to the design for an eradication programme:

- Thorough evaluation of the epidemiological situation in the region/country or area of focus (including identifying and controlling other relevant domestic and wild reservoirs, to minimise the risk of reintroduction of infection).
- Correct choice of the relevant epidemiological unit, e.g. a largely closed integrated poultry company or closed primary pig breeding herds, and sound epidemiological parameters.
- Effective control (decrease in the prevalence of infection) of the disease as a preliminary step towards eradication.
- The authorities and other players involved in the programme need to be clear on their respective responsibilities and an appropriate legislative framework for the programme must be established together with an administrative team with sufficient and proportionate financial resources for the running of the programme.
- Training at the appropriate level is mandatory for all relevant parties (awareness campaign targeted at farmer participants)—all involved stakeholders should clearly understand the tasks and duties involved.

Eradication can be successfully achieved in poultry production systems, as “all-in-all-out” production facilitates a clean break between flocks. For diseases where the risk of transmission between herds is high, control/eradication should preferably be done on an area/region/country-level.

**Zoning and compartmentalisation** (including SPF) are disease management strategies that pursue essentially the same objective: to establish animal populations with distinct health status, based on effective separation of populations of different status and application of biosecurity measures to prevent the introduction of infection. Zoning relies more heavily on geographic factors, such as natural or human-made barriers, while compartmentalisation focuses more on management and biosecurity within the establishments comprising the compartment, to ensure the maintenance of health status.

The SPF system can be cost-effective: less medication is needed and vaccination costs are reduced. It does depend on strict biosecurity and a closed herd policy or strict sourcing and transportation from controlled herds with similar health status. The impact of the SPF system will be greatest in farms towards the top of the breeding pyramid (for example, grandparent and parent broiler stock) (EMA and EFSA 2017).

As an example can be mentioned Danish system of the special SPF status in pig sector, that ensures the SPF herds are declared for a number of diseases, including mycoplasma, pleuropneumonia, swine dysentery, mange, lice and atrophic rhinitis. SPF herds can only be established by total depopulation, when the previous herd has been slaughtered and the whole unit is cleaned, disinfected and left empty for a specific period, until the introduction of SPF animals. The security of the system is based on a high level of biosecurity and close veterinary supervision. SPF herds may carry one of the above diseases, but, in this event, the herd may remain an SPF herd but with a qualification, e.g. SPF + ms (SPF with mycoplasma).

Currently, around 75% of all sows and 38% of finishers in Denmark have SPF status and 75% of Danish pigs are born in the SPF system (DAFC 2018). Many other herds operate to similar rules and standards, although they do not have the formal SPF accreditation (DAFC 2017).

**SPF Health rules for Danish pig farms requirements:**

- Protection against infection
  - Receipt and delivery of pigs, distance to neighbouring herds, visitors, deliveries of feed and litter
- Health inspection
  - Daily inspection by personnel
  - Monthly inspection by external veterinaries, reporting of undesirable symptoms
  - Monthly/annual testing of blood samples: Analysis of:
(i) Pleuropneumonia
   \textit{(Actinobacillus pleuropneumoniae)}
(ii) Enzootic pneumonia
    \textit{(Mycoplasma hyopneumoniae)}
(iii) Dysentery
    \textit{(Brachyspira hyodysenteriae)}
(iv) Salmonella
(v) Rhinitis
(vi) PRRS

- Purchase of pigs
  - With known health status
- Transport of pigs to herd
  - In approved SPF vehicles which are owned by a carrier approved by SPF-SuS

4.2 Smart and Precise Farming

Modern, computerised and artificial intelligence technologies also are currently coming to the farming. They can be considered as another, recently introduced disease management strategy. Different sensors such as remote sensors: cameras, microphones, thermometers and accelerometers and/or sensors touched to the body of animals like podometers, collars, thermometer ear sensors, vaginal sensors, tail (chip) implants/sensors, detection bolus in rumen, heart function sensors, monitor or capture information such as images, sound, heat or motion from groups or individual animals. The data from the sensors can be either stored (internally/externally, e.g. on clouds) or sent directly to a specific node for further processing. Processing is usually performed as software algorithm used to solve an individual task/issue or cluster of tasks/issues. Then transformation to the “outcome message” that can be translated should be done (e.g. in the case of podometer to evaluate if the cow has troubles with lameness). Computers can evaluate large scale of situations/examples either automatically or semi-automatically and learn from sets of examples comparing them to the measured/existing data. Computerised systems allow to process and analyse large data sets to track variables and produce estimates at a rate that would not be possible for humans or conventional (individual) statistical methods. Integrated, processed and analysed data can provide credible information and alerts regarding animal health, welfare and productivity (Table 5).

4.3 Alternative Tools

Despite the main purpose of this book targeted mainly on the use of antimicrobials in animals, in the era of growing issue of antimicrobial resistance, when conventional treatment strategies using antimicrobials have become ineffective due to the occurrence of drug-resistant bacteria, focus must be shifted towards alternative tools or therapies for prevention and treatment of infection diseases. Also consumers’ pressure and worries towards harmful effects of antibiotic use on produced food and the ban of antibiotics in the EU have prompted researchers to think about alternatives to antibiotics (Diara and Malouin 2014; EMA and EFSA 2017, ASOA 2017).

Although some alternatives have been already investigated also for use in food-producing animals, there are challenges the current research, regulatory bodies as well as veterinarians and farmers in practice are faced with and that make hard to implement them successfully in real practice.

Another aspect of alternative tools is lack of the proof of evidence that they are working effectively either as treatment options or prevention tools without any significant harmful effect that can lead to conclusion that risks/uncertainty outweigh the benefits from the alternative use. The majority of the studies that were identified in search by authors of RONAFA report (EMA and EFSA 2017) failed to meet one or more of the inclusion criteria. Most of the articles focussed on the effect of the potential alternative to antimicrobials on performance and did not include health parameters as end points of the studies. In a few studies, a comparison with an antimicrobial treatment was reported, mainly in the context of antimicrobials used as growth promoters and not within the context of the treatment of acute disease outbreaks.
Table 5  Examples of smart/precise farming technologies for pig, dairy cattle and poultry

| Animal species | Parameter                              | Brief description/detecting tools                                                                                                                                                                                                                                                                                                                                 |
|----------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pigs           | Lameness and reduced mobility          | In groups, sows with non-resolved lameness were observed to move and stand less, lie down more, and were in contact with the wall more than healthy control sows These differences in behaviour could be interpreted as signs of pain or as a way of seeking shelter and isolation from the group. Pressure force plate systems measurement of pressure distribution of claws, weight distribution on all four legs of sows and leg loading and weight shifting. Pressure mat measurement of maximum pressure, stride length, stance time, stride time, and activated sensor count per foot in both sows and weaned pigs. Imaging Motion tracking between frames from video consecutive images, a lateral motion path is calculated and compared to the actual forward movement of each sow. Accelerometers Devices attached to the leg of sows to detect posture and stepping behaviour, standing duration, latency to lie down after feeding, and step frequency when feeding and from pre-parturient nesting activity, detected the onset of farrowing. Ear detectors can indicate from high activity (distance walked) and rest phases (lying down) signs of lameness. Pen-level activity monitoring For welfare improvement and automate pig health monitoring. Imaging (including 3D imaging) Video images to measure pen-level activity such as antagonistic behaviours, chasing, tail and flank biting, fighting, head-to-head knocks between pigs. Depth imaging tracking to monitor pig location, eating, drinking and aggression interactions between pigs. 3D cameras and machine learning to detect pig activity and provide an automatic warning of tail biting "outbreaks". Sensor data differentiation of lying patterns of pigs (thermal comfort behaviour), standing pigs from moving pigs, and lateral from sternal recumbency. |
|                | Temperature/illness detection          | Infrared thermography is used at skin measurement sites for pigs, with the highest correlation to body temperature, are the ear base, eyes and udder, can also detect individual illness in groups of piglets. Vaccination is known to initiate high skin temperatures and huddling responses were observed up to 20 hours post vaccination of piglets. |
|                | Sound signals detection                | Microphones/vocal sensors/analysers To detect heat stress and high frequency “screams” of pain as a consequence of tail biting or fighting. Distinguishing between infectious productive coughs and non-infectious, non-productive coughs (ammonia or dust) from differences in the acoustic variables, enabling treatment for respiratory disease and ventilation changes at a pen level. In noisy barns or with insufficient microphones, detection level is limited. |
|                | Live weight, shape, growth and body composition measurement | Crucial factors in the management of swine production because individual pig weight and growth affects the herd in factors such as barn flow and space allowance, and audit parameters. Imaging/extracting the 3D shape of pigs for automatic mass and weight estimations. |

(continued)
Despite the difficulties identified, from the advancements within biotechnology, genetic engineering and synthetic chemistry, but also research of the substances occurred in natural products, seems that new perspectives are coming to be opened up towards the discovery of the alternatives to antimicrobials and preventive alternative tools. While some promising alternatives appear, thanks to the enormous effort especially in human medicine research, on veterinary side some of the new alternatives are kept out of practice also from the reason of high costs comparing to conventional therapies.

**Table 5** (continued)

| Animal species | Parameter | Brief description/detecting tools |
|----------------|-----------|-----------------------------------|
| Dairy cattle   | Measurement of heat in certain body parts | Infrared Thermography  
Non-invasive detecting of dissipation of heat in individual animals or specific regions of the body for the purpose of rapidly detecting diseases such as mastitis, locomotion disorders, and respiratory disease in bovine. |
|                | Body condition scoring | Several parameters can describe health/body condition  
3D Imagination  
Lower back image (loin, rump, hook, tailhead, fatness) |
|                | Oestrus, feeding and health signs | Activity, behaviour and health signs detection  
Accelerometer (3-axial accelerometer)  
Different technologies using ears, leg (podometers/accelerometers) or neck detectors (collar located) measuring activity |
|                | Lameness | Time and pressure sensors  
Stepmetric, podometers  
Platform/mat for gait consistency |
|                | Mating alert | Heat detector  
(Special belt) that detects standing or cow mounts in heat, the device send an SMS to the inseminator and saves records on the web |
|                | Calving process | Vaginal device with thermistor  
Measurement of the vaginal temperature  
Tail sensors (e.g. ring with accelerometer) |
|                | Rumen functions | Rumen bolus with pH electrode and thermistor  
Measurement of pH, temperature, drinking |
|                | Integrated (rumen activity, oestrus, drinking, temperature) | 3-axial accelerometer, thermistor |
| Poultry        | Welfare evaluation laying hens/chickens | Image analysis  
Thermometer and relative humidity sensors, carbon dioxide and ammonium detectors, luxmeters  
Monitoring temperature, humidity, air speed, CO₂, ammonium and light measurement, to ensure balanced conditions for birds (importance of sensors location at levels of living birds) |
|                | Thermal comfort/heat loss in chickens | Noise/vocalisation analysis  
Correlation between bird grouping pattern and vocalisation during thermal stress exposure  
Thermal imaging in chickens/hens  
Infrared thermography evaluation of groups of birds |
|                | Chick performance | Imaging technologies  
Captured images were analysed using raster image analysis software to determine the body surface area and a linear equation to estimate weights |

Modified according Benjamin and Yik (2019); Lokhorst (2018); Berckmans (2014)
Table 6 Examples to the various existing/promising alternatives or alternative tools that can help prevention or treatment of infectious diseases

| Alternative                      | Comments                                                                                                                                 |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Vaccines (examples)              | Inactivated, attenuated, recombinant, autogenous—see subchapters above for more details.                                                   |
| Vaccine adjuvants                | Adjuvants are crucial components of vaccines as they reduce the amount and number of doses required to elicit effective immunity. Three-component adjuvant contained a Toll-like receptor agonist, either polyclonal (poly-c) or CpG oligodeoxynucleotide, a host defense peptide and polyphosphazene. |
| Probiotics                       | *Lactobacillus spp.*, *Bacillus spp.*, *Enterococcus spp.*, *Bifidobacterium spp.*, *Lactococcus spp.*, *Pediococcus spp.*, *Streptococcus spp.*, *Propionibacterium spp.*, *Saccharomyces* spp. are the most commonly used, but some strains under the scrutiny because AMR transfer. |
| Prebiotics                       | Galactooligosaccharides                                                                                                                                                                       |
| Phytogenic feed additives        | Directly inhibit bacterial growth by inhibiting cell membrane functions As an immunostimulants plant polysaccharides (algae polysaccharides, *Astragalus* polysaccharide, chitosan, ganoderan, lentinan, *Polyergus* polysaccharide). |
| Essential oils                   | Terpinen-4-ol (from tea tree) inhibits pro-inflammatory cytokine, upregulates anti-inflammatory cytokine expression, and displays tissue healing characteristics in mastitis. |
| Phyto-extracts                   | Extracts from *Allium sativum* also exhibits antibacterial, anti-diarrhoeal, anti-inflammatory, and immune-modulatory properties.                                                             |
| Polyphenols                      | Antioxidant, anti-inflammatory, anticancer and antimicrobial properties of diferuloylmethane, a polyphenol isolated from turmeric (*Curcuma longa*) rhizomes.                                          |
| Organic acids                    | Different short-chain fatty acids, medium-chain fatty acids and other organic acids and their salts (e.g. formic acid, acetic acid, lactic acid, propionic acid, butyric acid, sorbic acid, benzoic acid) have been tested in animal nutrition. While the mode of action of organic acids for feed preservation and water hygiene mainly reflects pH reduction, their role in the gut is still not completely elucidated. |
| Amino acids                      | As an immunostimulant (arginine, leucine), cytosine-phosphate-guanine (CpG)-based immunostimulant.                                                                                             |
| CRISPR/Cas9                      | Clustered regularly interspaced short palindromic repeats-Cas are designed to cleave plasmids carrying AMR and virulence genes (gene silencing) or gene editing (insertion of a new sequence)—working on a selective site and creates a double stranded nick in the DNA, modifying or permanently replacing the target sequence. Can have potential application in controlling AMR at dairy farms, through application of, e.g. sprays/liquids on farm environment, dairy personnel hands. |
| Bacteriophages                   | Lytic phages are used, mostly still at research phase except topical products. Genetic engineered phage-based delivery system as an antimicrobial against *Staphylococcus aureus*—able to overcome the current shortcomings in phage-based delivery systems such as inefficient delivery, narrow host range, and potential transfer of virulence genes exist. Purified phage genes products like endolysins are used e.g. against *S. aureus*. |
| Bacteriocins                     | Directly inhibit bacterial growth by inhibiting cell membrane functions or inhibiting gene expression and proteosynthesis (nisin and lysostaphin inhibition of *S. aureus*—mastitis supportive therapy/teat sealant inclusion). Lacticin effective against *S. aureus, S. dysgalactiae*, and *Streptococcus uberis* Promising microcins and colicins isolated from specific *E. coli* strain against enteral infections of calves. |
| Bacterial extracts               | As an immunostimulant β-glucan, peptidoglycan, lipopolysaccharides, muroetasein, prodigiosin.                                                                                                      |
| Bacterial predators              | Gram-negative bacteria *Bdellovibrio bacteriovorus* and *Micavibrio aeruginosavorus* attack and kill certain pathogenic bacteria: as e.g. multiresistant *E. coli, Klebsiella spp.*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* (at the stage of in vitro studies). |

(continued)
Table 6 provides an introduction and also examples to the various existing/promising approaches that can, either solely, or in certain cases in combination with rational/minimal use of antimicrobials, help to keep animals healthy.

| Alternative                        | Comments                                                                                                                                 |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Engineered peptides               | Antibacterial, antifungal, antiviral. Directly inhibit bacterial growth by inhibiting cell membrane functions, the issue of practical application is related to instability, but also toxicity concerns and AMR. Under research and development are structurally nanoengineered antimicrobial peptide polymers could be a low-cost and effective against Gram-negative bacteria. |
| Nanoparticles                     | Metal based—blockage of enzyme pathways, alteration of cell wall, and nucleic material pathways. Research targeted on being explored as vehicles for delivery of antimicrobial agents. Nitric oxide and tilmicosin-solid lipid nanoparticles as well as silver in nanoparticles were investigated against S. aureus and mastitis prevention. |
| Immunomodulators/immunostimulants | Directly enhance innate immune responses through the activation of phagocytes, neutrophils, alternative complement system, and increased lysozyme activity. Typical representatives are biological cytokines as interferon, transfer factor, interleukin, immunoglobulins. Chemically synthesised (cimetidine, imiquimod, levomisole, pidotimod, polyinosinic acid, sodium houttuynonate, tilorone, ubenimex). |
| Antibodies (IgY)                  | IgY is a major serum immunoglobulin in birds and is available in high concentration from chicken egg yolk. Promising tools in GIT infections (rotavirus in animals neonates), orally administrated immunoglobulin Y has been used to prevent or treat bacterial and viral diseases in mammalian, avian and aquatic species. The antibodies in the egg or the yolk can be incorporated into diet, prepared in dry form by spray- or freeze-drying, but the best technology proven is encapsulation [nanocomposite matrix] |
| Vitamins                          | As an immunostimulant (A,E,C)                                                                                                                                                                          |
| Minerals                          | As an immunostimulant (Se, Zn), new technologies like lipid encapsulated low concentration zinc occurred.                                                                                                                                                      |
| Enzymes                           | Used in feed additives. Carbohydrates (e.g. amylases, glucanases, cellulase, invertase) Lipase, Proteases (bromelain, papain, trypsin, pepsin), oxidoreductases, phosphatase acting not only by affecting the feed and its digestibility, but interacting also with minerals and influencing also the production and secretion of mucin, which influence the organisation of intestinal epithelial surface and eventually microbial composition of the gut. Also can have an impact on microbial population by providing selective nutritional components to specific group of microbes. Also effects on innate immunity. |
| Quorum sensing inhibitors/quorum quenchers | Could control virulence of pathogens by inhibiting the binding of auto-inducers to respective receptors. QSIs have been classified into peptide (autoinducing peptide homologs), protein QSIs, and non-peptide small molecules, can interfere with QS signal molecule synthesis or their binding to the receptor. |

Modified, amended according: Mehdi et al. (2018), Marquardt and Li (2018), Sharma et al. (2018), Garg et al. (2017), Park et al. (2017), Kovacs-Nolan and Mine (2012), Bikard and Barrangou (2017), Li et al. (2017), Jiang et al. (2017), Hassanein and Soliman (2010), Nava et al. (2009), Bednarczyk et al. (2016), Mohammadaghert et al. (2016), Rasschaert et al. (2016), EMA and EFSA (2017)

5 How the Welfare Can Help to Keep Animals Healthy and Free from Infectious Disease

As the antimicrobials serve the possibility to treat the diseased animals, it can be anticipated that
healthy animals do not need them. The OIE’s formal recognition of the scientifically proved critical relationship and connection between animal welfare and animal health, and the resulting development of the international recommendations set out in the OIE Code, provide strong evidence of the growing consensus on the importance of animal welfare standards. There are available scientific papers that give the evidence of compliance with animal welfare standards strengthens both the health of farm animal populations (including their resistance to disease outbreaks) and the quality of animal food products. Animal welfare science identifies a number of common areas of synergy between animal welfare, animal health and productivity (Fraser 2006).

Ensuring Good animal welfare is the farmer/animal owner/vet responsibility that includes consideration of all aspects of animal well-being, including proper housing, management, nutrition, disease prevention and treatment, responsible care, humane handling and, when necessary, humane euthanasia (AVMA 2019).

Animal welfare reflects how well an animal is coping with the conditions in which it lives. Animals have good welfare if they are healthy, comfortable, well-nourished, safe, able to express the natural behaviours of their species and are not suffering from unpleasant states such as pain, fear and distress.

As an essential prerequisite following Five Freedoms rules were defined and well characterised animal welfare principles (Mellor 2016):

1. Freedom from hunger and thirst—by ready access to fresh water and a diet designed to maintain full health and vigour
2. Freedom from discomfort—by the provision of an appropriate environment including shelter and a comfortable resting area
3. Freedom from pain, injury or disease—by prevention or through rapid diagnosis and treatment
4. Freedom to express normal behaviour—by the provision of sufficient space, proper facilities and company of the animal’s own kind
5. Freedom from fear and distress—by the assurance of conditions that avoid mental suffering

There has been also released WQP criteria for the assessment of animal welfare as follows (according Vapnek and Chapman 2010):

Criteria
1. Animals should not suffer from prolonged hunger, i.e. they should have a sufficient and appropriate diet.
2. Animals should not suffer from prolonged thirst, i.e. they should have a sufficient and accessible water supply.
3. Animals should have comfort around resting.
4. Animals should have thermal comfort, i.e. they should neither be too hot nor too cold.
5. Animals should have enough space to be able to move around freely.
6. Animals should be free from physical injuries.
7. Animals should be free from disease, i.e. farmers should maintain high standards of hygiene and care.
8. Animals should not suffer pain induced by inappropriate management, handling, slaughter or surgical procedures (e.g. castration, dehorning).
9. Animals should be able to express normal, non-harmful social behaviours (e.g. grooming).
10. Animals should be able to express other normal behaviours, i.e. they should be able to express species-specific natural behaviours such as foraging.
11. Animals should be handled well in all situations, i.e. handlers should promote good human–animal relationships.
12. Negative emotions such as fear, distress, frustration or apathy should be avoided, whereas positive emotions such as security or contentment should be promoted.

As mentioned also in RONAFA (EMA and EFSA 2017) current research focusses on
animal-based measures (ABMs) which are directly linked to an animal’s response to adverse circumstances (as opposed to non-animal-based measures which describe the situation in which they are kept, and only indirectly represent the effect they may have on the animal) (Welfare Quality 2009). ABMs include physiological parameters (such as the stress hormones—see below for stressors), behavioural parameters (aggression, restlessness, but stereotypies, social withdrawal and apathy), as well as the actual appearance of the animal (skin lesions, clinical signs of illness, overall health status). Of great importance is minimising of stressors that can be listed in relation with currently used (intensive) farming technologies as well as animal movements: heat, cold, improper air ventilation (too much ammonia, hydrogen sulphide, carbon dioxide), lighting, crowding, mixing of animals from different sources, farrowing/hatching/calving, weaning and animals separation (calves/piglets), limit-feeding and water supply, insufficient bedding, improper milking, noise, pests and parasites and restraint. Improvement of human–animal interaction (handling), enrichment (environment that provides complexity, manipulability and cognitive stimulation of animals), prevention of abnormal behaviours (such as tail biting in pigs, prevention of feather pecking and cannibalism), minimising pain and stress in painful procedures (tail docking, teeth clipping or grinding, nose ringing), and proper transportation conditions can significantly improve welfare of animals. Detailed information on animal welfare specified for pigs, chickens, beef cattle, dairy cattle and working equids are described in OIE (2019), Terrestrial Animal Health Code, Section 7. All of these stressors, even not in a same scale, have been shown to alter the immune system of animals.

Despite the commonly accepted fact that ensuring animal welfare can help to keep animals healthy, also another aspect should be taken into account in current days, where, under extreme pressure to minimise the use of antimicrobials or even ban of some antimicrobials, can appear the situation, in which sick animals will not be properly treated, what can hamper animal welfare. Also consumers’ increasing demand on raising animals without antibiotic (i.e. antibiotic-free production avoiding any use of them) can provoke the questions on sustainability of such systems as well as impact on animal welfare (Cervantes 2015; Karavoilas et al. 2018). Banning or severely restricting the use of antimicrobials in animals may negatively impact the veterinarian’s ability to protect animal health and prevent suffering from disease, which could potentially lead to worsening of welfare as well as finally lower quality of food from food-producing animals. Current works as e.g. Kruse et al. (2019) commented on association between the antimicrobials use and lesions at slaughter that were found. The authors of study concluded that prevalence of lesions was slightly (non-significant) higher in pig herds with no registered antimicrobial use than with prescriptions of antimicrobials. In another study increasing incidence of eye burns, footpad lesions and airsacculitis in chicken broilers has been documented for broiler flocks with no use of antimicrobials (Karavoilas et al. 2018). Therefore, rational, evidence-based approach should be used when handling antimicrobials—i.e. use them only in cases when necessary, but in sufficient dose, intervals and duration.

Summarising above facts, in relation to use of antimicrobials in food-producing animal husbandries, animal welfare improvement can serve as a potent tool for improvement of animal immunity and health, that in the end will lead with no/low need to use antimicrobials. On the other hand too strict restrictions of antimicrobial use, without considering actual situation at each individual farm and condition, can lead to negative impact on animal welfare. Balanced, rational and responsible approach should be therefore chosen by vets in cooperation with farmers.

6 Socio-economical Aspects to Be Considered

Production of the food commodities (mainly meat, eggs and milk) contribute in a large scale to cover the need of proteins and generally food
demand by human population. Within the European area, well supplied by food, ethical food consumption strategies raised during last years (Miele and Evans 2010), which are supported by appropriate regulatory and infrastructural regimes (Davies et al. 2013). Currently more and more consumers thinking on animal welfare and are aware of the resistance issue, also environmental questions are raised with increased frequency. Call for changes or improvement of the farming sector to sustainable and nature-friendly production, that ensure safe food has become urgent.

Previous chapters have shown that antimicrobial use in food-producing animals technologies of production are influenced by several types of drivers (Collineau 2016); these include not only technical drivers, e.g. 1-day-old chicks and piglets health status (van Rennings et al. 2015, prudent use GL), vaccination schemes or biosecurity level (Rojo-Gimeno et al. 2016), but also psychosocial drivers that are related, among others, to farmers’ and veterinarians’ attitudes and habits towards antimicrobial usage (Visschers et al. 2016; Coyne et al. 2016). The relative importance of technical versus psychosocial drivers seems to be critical for setting of the well balanced policies.

Views on the aspects/drivers influencing the use of antimicrobials to be considered can be from different perspectives. One of the examples can be RESET Mindset Model (Lam et al. 2017) that contains the most important cues to change human behaviour, being Rules and regulations, Education and information, Social pressure, Economics, and Tools.

6.1 Regulatory/Legal/Rules Setting

Non-binding documents: Different documents can be adopted globally—usually as resolutions, guidelines and recommendations (e.g. Codex Alimentarius level, OIE level), creating global consensus, but should be implemented voluntarily. Similarly that can be done at the European level (e.g. Prudent Use Guidelines or AMR resolutions) or at National level (National Action plans—depending on exact way of approval and making certain steps obligatory by, e.g. national legal provisions). The main issue with such documents is that they create rather “general policies”, partly raising awareness and make global societal pressure, but, according to the book author opinion, are not leading directly to change of the behaviour in everyday practices of farming. Despite this, without global consensus and recognising AMR as a threat and releasing the signal of importance to find solution, further more pragmatic steps could remain isolated.

Legally binding documents: Depending on the cultural habits and traditions, such setting of obligatory and many times also restrictive or at least prescriptive rules could be helpful. At the European level—new regulation on veterinary medicinal products, at national level several examples can be listed: national law on mandatory susceptibility testing (mainly prior critically important antimicrobials to be used); national law banning the profit from sales of antimicrobial veterinary medicinal products by vets; national law setting the specific taxes on antimicrobials; national law on benchmarking (and further measures mainly targeted on those exceeding the thresholds) etc. Setting of such legal rules should be accompanied with both educational/motivation/stimulation activities as well as checking activities (unfortunately not only supervision, but also system of penalties/punishments).

6.2 Social Pressure

From public health/one health perspective social pressure can increase due to the raising of awareness of the whole society, but also is more targeted on smaller group of interested parties. Among powerful tools belong campaigns that show current antimicrobial consumption at least per animal production sector and also set the targets for (rational) reduction.

With respect to responsible use of antimicrobials, vets and other consultants play an important role in shaping this societal frame of reference, because they have a strong influence on farmers’ opinions about animal health. In
many cases, veterinarians decide whether to treat an animal or not with antimicrobials, select the antimicrobial to be used, as well as define the dosage and route of administration. Veterinarians also advise farmers on animal health (including vaccination programmes), biosecurity and production management issues that can strongly influence animal health and finally also the need for use of antimicrobials and the transmission of resistant bacteria. Considering vets role, of importance are setting, e.g. recommendation for preventive health programmes (e.g. rules for setting of husbandry tailored vaccination schedules based on epidemiologic evidence) and also first, second and last choice of antimicrobials, altogether with availability of benchmarking that can strengthen the stimulation “not to be worse than my neighbours”. Farmers are also a key stakeholders from the farm management, biosecurity, animal health, and welfare perspective, based on everyday experience and contact with animals, they can identify risk factors (and consequently intervene) associated with issues of their animals and husbandry issues and finally also influence the need for use of antimicrobials in livestock. Example of specific attitudes and characteristics of sow farmers, who use less antibiotics (Bergevoet et al. 2019) is given in Table 7.

Applying social psychology to Antimicrobial prescribing practices several models have been described yet. Using of the TPB theory of planned behaviour (Ajzen 1991) to intensive farming of food-producing animals, that identified three most important determinants of behaviour, was one of them:

| ATTITUDE                  | Is the behaviour good to do? |
|---------------------------|-----------------------------|
| SUBJECTIVE NORMS          | What do other actors expect me to do, and do I care what they think? |
| PERCEIVED BEHAVIOURAL CONTROLS | How easy or difficult is the behaviour for me to do? |

Change of behavioural models create the up to date approach, how to influence animal health and welfare and finally change/decrease antimicrobials use patterns. There has been recognised steps to be followed for behaviour change and coaching approach has been applied in certain studies yet. Model applicable for farmer/vet is indicated in Fig. 1.

One of the change management models already well incorporated in corporate business is the ADKAR® model. This model identifies the five different elements essential for the successful implementation of change: Awareness, Desire, Knowledge, Ability and Reinforcement and allow the scoring of the individual model parts. Very recent study presented by Caebcke (2019) shows that after a first coaching session, the average ADKAR scores increased, meaning that the farmers changed behaviour to more prudent antimicrobial use after only 6 months. It should be noted that those farms already achieved large reduction in the amount of antimicrobials used, but this specific action plan can further help in reducing the use of antimicrobials by

Table 7 Characteristics of attitudes of the sow farmers who use less antibiotics (according Policy paper, Economics of antibiotic use, Bergevoet et al. 2019)

| Have a higher intention to get or keep the usage of antibiotics under the target value and are more positive about it. |
|----------------------------------------------------------|
| Think that less usage of antibiotics increases work pleasure and is good for animal health, animal welfare and human health. |
| Think to a lesser extent that farm results will get worse if they reduce the usage of antibiotics |
| Perceive less risk and uncertainty. |
| Perceive to have enough knowledge, time (and money) available to keep or get antibiotic usage under the target value. |
| Think that they use less antibiotics and that the health status of their farm is better when they compare themselves with other farms. |
| Are less negative about policymakers. |
| Think to a greater extent that other pig farmers, customers, the government, their partner and their neighbour find it important that antibiotic usage is low. |
focusing on improvements in biosecurity and the use of alternative tools.

### 6.3 Customers’ Demand

With raising awareness of the general public, related to risks associated with use of antimicrobials in food-producing animals there have also started to raise consumers’ worries related to residues of antimicrobials in food as well as antimicrobial resistance and pollution of the environment due to extensive use of veterinary antimicrobials. Also use of antimicrobials as growth promoters, still being administered to huge amount of animals in certain part of the world (except the EU) is of great consumer concern. For many years, many supermarkets failed to take the issue seriously. In the past couple of years, in particular emphasised also by the publication of the government-commissioned Antimicrobial Resistance Review—the “O’Neill Report” (O’Neill 2015), there has been a considerable amount of work happening behind the scenes in certain countries. One of the good examples to be mentioned is the activity of the head offices of the UK’s largest supermarkets. Agricultural teams, Corporate Social Responsibility teams and antimicrobial-resistance experts have been working together in a variety of ways to devise new policies to reduce antibiotic use in their supply chains. In more integrated supply chains (the poultry industry), it has been easier to get rapid shifts in practices, but for more fragmented sectors (cattle, pig, sheep), supermarkets need to deal with a much wider range of suppliers. Nevertheless, with some supermarkets we are starting to see new policies being introduced across all species (ASOA 2017). From certain period some of the supply
chains introduced the policy of requirement on primary producers as, e.g. they have banned to have in their nets products from husbandries with routine preventative use, introduce restriction policies as for the use of the critically important antibiotics, and some of them announced that will not trade the products from farms using of the last-resort antibiotic colistin. Some food chains have started to ask the primary producers also for data on use of antimicrobials and published the targets.

On the other hand, there exist the information “gaps” among food-producing industry—consumers and scientists to more explain the situation. Until these days there was not quantified the exact scale of participation of use of antimicrobials in animals on the extent of the issue of AMR in human medicine or more broadly in the environment. Also the explanatory/educational work is needed for not gaining the general perception that we can finally produce all food without any antimicrobials, as it will have an impact on animal health, welfare and finally also on human health through, e.g. possible spread of zoonotic diseases. There cannot be introduced false perception, that any animal will never get sick in the flock/herd and that the spread of infection in the groups or big herds/flocks on the farm can be easily blocked without any use of antimicrobials. Instead of it, as rational and responsible as possible approaches should be investigated, communicated with professionals (vets/farmers), explained to public and especially applied for using antimicrobials in animal sector on everyday basis.

6.4 Economy Pressure

The possible benefits from the use of antimicrobials in animals need to be balanced against their cost and the costs of application and the costs in humans and animals caused by increased risk of emergence of resistance, but also other risks (see also the Chap. 5). The picture should be viewed not only from the short-term perspective (i.e. one treatment course, or one course of fattening gains), but long-term perspective should be considered. For example, whilst antimicrobials may enhance the growth and efficiency of livestock, it could well lead over time to the emergence of resistance to antimicrobials and any outbreaks of disease of organisms with resistance genes would require the use of more expensive antimicrobials (either directly in animals, or consequently after spread of resistant microbes also in human). Conversely not using antimicrobial prophylactically may increase feed costs and perhaps costs associated with disease and death loss, but diseases are less likely to be caused by resistant pathogens and can often be treated with less expensive first-line antimicrobial drugs (Rushton 2015). There should be also counted not only direct costs, but also indirect costs (e.g. broad and extensive research needed to discover new effective antimicrobials). Work of Smith and Coast (2013) indicated that an increase in resistant organisms coupled with no new antibacterial discovered since 1987 (Davies et al. 2013), and very few antivirals and antifungals indicate a crisis.

Speaking about long perspective, there is clearly visible need for reduction of use of antimicrobials (to the minimum level needed for the treatment/justified metaphylaxis) that can be promoted also via economical tools. Some tools have been developed and already used, e.g. decoupling of veterinarians incomes and avoiding profit from prescription and selling of antimicrobials, or impose tax either on specific pharmaceutical form of antimicrobials (e.g. in Germany on medicated feed) or on certain group/s of antimicrobials (e.g. colistin or selected critically important antimicrobials as e.g. cephalosporins of third and fourth generation or fluoroquinolones). Also tax “incentives”, e.g. for vaccination, can be the option. More tricky is discovery and introduction to practice of effective and safe alternatives, that will be economically attractive. Also presentation of success in reduction of the use of antimicrobials as well as use of alternatives can be sources of the knowledge, but full information should be presented and explained and also equally highlighted. For example the policy paper issued by the Wageningen University (Bergevoet et al.
declaring and highlighting “The reduction in antibiotic usage on broiler and pig farms in the Netherlands from 2009 to 2017 did not result in a deviation from the long-term trend in average production and economic results in these sectors. To improve animal health, which made a reduction in antibiotic usage possible, farmers used a variety of relatively easy and cheap measures, such as more attention to hygiene, use of painkillers and anti-inflammatory agents or more preventive vaccinations.” should be more discussed considering all information meant in individual part of the report—as costs of enlarged vaccination programmes, cost of individualisation of care in sows, costs of modernisation/newly build premises (with improved air conditioning, water supply/water pipe systems of clean water), creating of separate sickbays for piglets and separate for sows, injection without needles, keeping breeding sows in quarantine, that are, as “proactive approach”, in complexity more expensive than “reactive approach”, i.e. use of antimicrobials. Also should be considered the resources (national government or EU interventions/incentives), e.g. building/reconstruction of new modern facilities.

In summary, some qualitative research showed that some pig farms managed to have simultaneously low antimicrobial use and high technical performance (Fertner et al. 2015); it would be interesting to explore how these “top farms” differ from the others in terms of health status, farm management practices and herd characteristics as well as for real economy parameters. This should contribute to better inform and target future risk mitigation strategies and accompany them with exact measures for practice. From the economical perspective the overview of measures and actions preventing/replacing the use of antimicrobials evaluated for their real costs will be beneficial. Performing thorough analysis of such data and finally providing the real picture for the economists as well as farmers will allow to choose farmers the most economically sustainable way of reduction of use of antimicrobials.

6.5 Education

There is the need for targeted education for professionals veterinarians/farmers/zootecnicians/feed mills/laboratory staff and other professional stakeholders. Education tailored for each level and role of individual professions in the system, that can influence level of awareness of AMR issue, set adequate level of knowledge of preventive programmes for animal health and welfare. For veterinarians specific set of trainings targeted on the continuous improvement of knowledge on disease prevention, vaccination programmes, diagnostics (including e.g. sampling techniques, precise farming technologies), advances in treatment options as well as recommendations for judicious and locally tailored evidence based use of antimicrobials seems to be beneficial. Also models targeted on change of behaviour frameworks and negotiation techniques (improving relationships/trust especially among farmers and vets) could help.

Awareness campaigns targeted on food processors/retailers but also on general public (including consumers explanatory campaigns) can bring improvement of common understanding of the issue.

Last but not least as for importance—involvement of the politicians and policy/decision makers influencing the legal and regulatory rules as well as socio-economical surrounding is necessary.

7 Concluding Remarks

Use of antimicrobials either via prophylaxis, metaphylaxis or treatment to solve the animal infectious diseases issues is reactive approach/solution. It has great benefits, considering especially acute outbreaks of diseases, where causative agent is still susceptible to antimicrobial of choice and animal/s can be successfully treated and protected from unnecessary suffering. In such case, once proper dose, duration and frequency of
treatment is chosen and the treatment start in the early stage of disease, we can, with the high probability say, that no alternatives, of the same potency, same effectivity and also same price are currently available. On the other hand, use of antimicrobials also pose significant risks (see Chap. 5) which cannot be overlooked. Rising awareness of antimicrobial resistance as the real threat that, in some cases, have already caused treatment failure both in human and animals lead the global society to ask for decreasing the use of antimicrobials and saving them for life-threatening infections of people. Therefore, increased need for tools of preventive medicine, need for establishing tailored herd/flock health programmes, that include also vaccination plans, ask for more strict following biosecurity and hygiene principles altogether with good husbandry practices keeping animals under good animal welfare seems to be vital. Big challenge is in front of research and development as for new alternatives to antimicrobials.

References

Ajzen I (1991) The theory of planned behavior. Organ Behav Hum Decis Process 50(2):179–211
Antonissen G, Martel A, Pasmans F, Ducatelle R, Verbrugghe E, Vandenbergrouck V, Li S, Haesebrouck F, Van Immerseel F, Croubels S (2014) The impact of Fusarium mycotoxins on human and animal host susceptibility to infectious diseases. Toxins 6(2):430–452
Arsenakis I, Boyen F, Haesebrouck F, Maes DGD (2018) Autogenous vaccination reduces antimicrobial usage and mortality rates in a herd facing severe exudative epidermitis outbreaks in weaned pigs. Vet Rec 182:744
ASOA (2017) Alliance to save our antibiotics: real farming solutions to antibiotic misuse, what farmers and supermarkets must do. Briefing 28 p. https://www.soilassociation.org/media/14072/asoarreal-farming-solutions-to-antibiotic-misuses-what-farmers-supermarkets-must-do-091117pdf. Accessed 22 July 2019
AVMA (2019) American Veterinary Medical Association: Animal welfare: seeing the forest and the trees. AVMA 6002482862. https://www.avma.org/KB/Resources/Reference/AnimalWelfare/Documents/animal_welfare_brochurepdf. Accessed 22 July 2019
Bednarczyk M, Stadnicka K, Kozlowska I, Abiuso C, Tavaniello S, Dankowiakowska A et al (2016) Influence of different prebiotics and mode of their administration on broiler chicken performance. Animal 10:1271–1279
Benjamin M, Yik S (2019) Precision livestock farming in swine welfare: a review for swine practitioners. Animals 9:133
Berckmans D (2014) Precision livestock farming technologies for welfare management in intensive livestock systems. Scientific and Technical review of the Office International des Epizooties 33(1):189–196
Bergevoet R, van Asseldonk M, Bondt N, van Horne P, Hoste R, de Lauwere C, Puister-Jansen L (2019) Wageningen economic research. Policy paper, Economics of antibiotic use, 2019-026. https://edepot.wur.nl/475403. Accessed 22 July 2019
Bernardini C, Grilli E, Duvigneau JC, Zannoni A, Tugnoli B, Gentilini F (2014) Cellular stress marker alteration and inflammatory response in pigs fed with an ochratoxin contaminated diet. Res Vet Sci 97:244–250
Bikard D, Barrangou R (2017) Using CRISPR-cas systems as antimicrobials. Curr Opin Microbiol 37:155–160
Borst LB, Mitsu Suyemoto M, Chen LR, Barnes HJ (2019) Vaccination of breeder hens with a polyvalent killed vaccine for pathogenic Enterococcus cecorum does not protect offspring from enterococcal spondylitis. Avian Pathol 48(1):17–24
Bossé JT, Li Y, Sárközi R, Fodor L, Lacouture S, Gottschalk M, Casas Amorbieta M, Angen Ø, Nedbalcova K, Holden MTG, Maskell DJ, Tucker AW, Wren BW, Ycroft AN, Langford PR, BRaDPIT Consortium (2018) Proposal of serovars 17 and 18 of Actinobacillus pleuropneumoniae based on serological and genotypic analysis. Vet Microbiol 217:1–6
Caekebeke N (2019) Use of a livestock-adapted ADKAR change management model for reducing AMU. AACTING Bern, p 1–31. https://aacting.org/swfiles/files/AACTING_Bern_Caekebeke_71.pdf. Assessed May 2020
Callaway TR, Edrington TS, Anderson RC, Harvey RB, Genovese KJ, Kennedy CN, Venn DW, Nisbet DJ (2008) Probiotics, prebiotics and competitive exclusion for prophylaxis against bacterial disease. Anim Health Res Rev 9:217–225
Catry B, Dewulf J, Maes D, Pardon B, Callens B, Vanrobaeys M et al (2016) Effect of antimicrobial consumption and production type on antibacterial resistance in the bovine respiratory and digestive tract. PLoS One 11(1)
Cervantes HM (2015) Antibiotic-free poultry production: is it sustainable? J Appl Poultry Res 24(1):91–97
Collineau L (2016) Quantify, explain and reduce antimicrobial usage in pig production in Europe. PhD Thesis. https://www.theses.fr/2016ONIR091F.pdf. Accessed 22 July 2019
Coyne LA, Latham SM, Williams NJ, Dawson S, Donald DJ, Pearson RB, Pinchbeck GL (2016) Understanding the culture of antimicrobial prescribing in agriculture: a qualitative study of UK pig veterinary surgeons. J Antimicrob Chemother 71(11):3300–3312. https://doi.org/10.1093/jac/dkw300
Coyne LA, Latham SM, Dawson S, Donald IJ, Pearson RB, Smith RF, Williams NJ, Pinchbeck GL (2018) Antimicrobial use practices, attitudes and responsibilities in UK farm animal veterinary surgeons. Prev Vet Med 161:115–126

Cyjetkovic V, Sipos S, Szabo I, Sipos W (2018) Clinical efficacy of two vaccination strategies against Mycoplasma hyopneumoniae in a pig herd suffering from respiratory disease. Porcine Health Manag 4:19

DAFC (2017) Pig industry quality manual, 5th edn, 1st issue. Danish Agriculture & Food Council, Copenhagen. https://www.lf.dk/-/media/lf/aktuelt/publikationer/svinekod/2018/qsg-english-2017.pdf?la=da. Accessed 22 July 2019

DAFC (2018) SPF system Denmark, CHR lookup. http://spfsus.dk/en. Accessed 22 July 2019

DANMAP (2014). http://www.danmap.org/Downloads/DANMAP.pdf. Accessed 22 July 2019

Davies DS, Grant J, Catchpole M (2013) The drugs don’t work. A global threat. Penguin, London

De Briyne N, Atkinson J, Pokludova L, Borriello S (2014) Antibiotics in Canadian poultry productions and anticipated alternatives. Front Microbiol 5:282

Dieste-Perez L, Frankena K, Blasco J, Muñoz S, de Jong M (2016) Efficacy of antibiotic treatment and test based culling strategies for eradicating brucellosis in commercial swine herds. Prev Vet Med 126:105–110

EFSA (2009) European Food Safety Authority: Panel on Animal Health and Animal Welfare, Scientific Opinion on the overall effects of farming systems on dairy cow welfare and disease. EFSA J 1143:1–38

EMA, EFSA (2017) European Medicines Agency and European Food Safety Authority: Joint Scientific Opinion on measures to reduce the need to use antimicrobials in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA). EFSA J 15(1):4666

EPRUMA (2019) European platform for responsible use of medicines in animals: best-practice framework for the use of vaccines in animals, 8 p. https://www.eprumaeu/wp-content/uploads/2019/04/Best-practice-framework-on-vaccines_23-APRIL-2019pdf.pdf. Accessed 22 July 2019

European Commission (2014) Discussion paper on Progress under the Animal Health Strategy for the European Union (2007–2013) where “Prevention is better than cure” and possible future steps. Directorate G – Veterinary and International Affairs Unit G2 – Animal health. https://ec.europa.eu/food/animals/health/strategy2007-2013_en. Accessed 22 July 2019

European Commission (2015) Guidelines for the prudent use of antimicrobials in veterinary medicine. Eur Official J, 2015/C 299/04. https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf. Accessed 22 July 2019

FAO (2010) Food and Agriculture Organization of the United Nations/World Organisation for Animal Health/World Bank. Good practices for biosecurity in the pig sector – Issues and options in developing and transition countries. FAO Animal Production and Health Paper No. 169, Rome

FAO (2019) FAO and Denmark Ministry of Environment and Food – Danish Veterinary and Food Administration: Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark. Rome. 52 pp. Licence: CC BY-NC-SA 3.0 IGO

Federation of Veterinarians of Europe (2016a) Antimicrobial use in food-producing animals, FVE input to RONAFÖ report. EFSA J 15(1)

Federation of Veterinarians of Europe (2016b) Relationship between animal welfare and the use of antibiotics in food animals. https://www.fve.org/cms/wp-content/uploads/063-FVE_AWW-Position-on-resistance-and-animal-welfare_final.pdf. Accessed 4 June 2019

Fertner M, Sanchez J, Boklund A, Stryhn H, Dupont N, Toft N (2015) Persistent spatial clusters of prescribed antimicrobials among Danish pig farms – a register-based study. PLoS One 10:e0136834

Fraser D (2006) Animal welfare assurance programs in food production: a framework for assessing the options. Anim Welf 15:93–104

Friedman D, Kanwat C, Headric M, Patterson N, Neely J, Smith L (2007) Importance of prudent antibiotic use on dairy farms in South Carolina: a pilot project on farmers’ knowledge, attitudes and practices. Zoonoses Public Health 54:366–375

Garg R, Babiuk L, van Drunen Littell-van den Hurk S, Gerds V (2017) A novel combination adjuvant platform for human and animal vaccines. Vaccine 35 (Pt A):4486–4489

Hampson DJ (2018) The spirochete Brachyspira pilosicoli, enteric pathogen of animals and humans. Clin Microbiol Rev 31:e00087-17. https://doi.org/10.1128/CMR.00087-17. Accessed 22 June 2019

Hassanein SM, Soliman NK (2010) Effect of probiotic (Saccharomyces Cerevisiae) adding to diets on intestinal microflora and performance of hy-line layers hens. J Am Sci 6

Hoelzer K, Bielke L, Blake DP, Cox E, Cutting SM, Devriendt B, Erlacher-Vindel E, Goossens E, Karaka K, Lemiere S, Metzner M, Raucek M, Colrell Suriñach M, Wong NM, Gay C, Van Immerseel F (2018a) Vaccines as alternatives to antibiotics for food producing animals. Part 1: Challenges and needs. Vet Res 49(1):64

Hoelzer K, Bielke L, Blake DP, Cox E, Cutting SM, Devriendt B, Erlacher-Vindel E, Goossens E, Karaka K, Lemiere S, Metzner M, Raucek M, Colrell Suriñach M, Wong NM, Gay C, Van Immerseel F (2018b) Vaccines as alternatives to antibiotics for food producing animals. Part 2: New approaches and potential solutions. Vet Res 49(1):70

Jensen VF, de Knegt L, Andersen VD, Wingstrand A (2014) Temporal relationship between decrease in antimicrobial prescription for Danish pigs and the “Yellow Card” legal intervention directed at reduction of antimicrobial use. Prev Vet Med 117:554–564
Jiang Y, Zheng W, Kuang L, Ma H, Liang H (2017) Hydrophilic phage-mimicking membrane active antimicrobials reveal nanostructure-dependent activity and selectivity. ACS Infect Dis 3:676–687

Jorge S, Dellagostin OA (2017) The development of veterinary vaccines: a review of traditional methods and modern biotechnology approaches. Biotechnol Res Innov 1:6–13

Karavolias J, Salois MJ, Baker KT, Watkins K (2018) Raised without antibiotics: impact on animal welfare and implications for food policy. Transl Anim Sci 2 (4):337–334

Kontturi M, Janni R, Simojoki H, Malinen E, Seuna E, Klitgaard K, Kujala-Wirth M, Soveri T, Pelkonen S (2019) Bacterial species associated with interdigital phlegmon outbreaks in Finnish dairy herds. BMC Vet Res 15(1):44

Kovacs-Nolan J, Mine Y (2012) Egg Yolk Antibodies for Passive Immunity. Annu Rev Food Sci Technol 3 (1):163–182

Kruse AB, Kristensen CS, Lavlund U, Stege H (2019) Mindset Model applied on decreasing antibiotic usage in dairy cattle in the Netherlands. Ir Vet J 70:5

La T, Phillips ND, Hampson DJ (2019a) An atypical weakly haemolytic strain of Brachyspira hydysenteriae is avirulent and can be used to protect pigs from developing swine dysentery. Vet Res 50 (1):47. https://doi.org/10.1186/s13567-019-0668-5

La T, Phillips ND, Hampson DJ (2019b) Vaccination of chickens with the 34 kDa carboxy-terminus of Bpmp72 reduces colonization with Brachyspira pilosicoli following experimental infection. Avian Pathol 48(1):80–85

Lam TJGM, Jansen J, Wessels RJ (2017) The RESET Mindset Model applied on decreasing antibiotic usage in dairy cattle in the Netherlands. Ir Vet J 70:5

Li J, Koh JJ, Liu S, Lakshminarayanan R, Verma CS, Beuerman RW (2017) Membrane active antimicrobial peptides: translating mechanistic insights to design

Lokhorst C (2018) An introduction to smart dairy farming. Van Hall Larenstein University of Applied Sciences, 108 p. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=13&ved=2ahUKEwiOw4mO6sjAhXwww8QBHdzhCNcQFjAMegQIAXAC&url=https%3A%2F%2Fwww.greenin.nl%2Fwebopac%2FMetaDataEditDownload.csp%3Ffile%3D%23%3A144032%3A1&usg=AOvVaw2rlyOpFA2ejzJnEHagR97S. Accessed 28 June 2019

Marquardt RR, Li S (2018) Antimicrobial resistance in livestock: advances and alternatives to antibiotics. Anim Front 9(2):30–37

Mehdi Y, Létourneau-Montminy MP, Gaucher ML, Chorfi Y, Gayatri S, Rouissi T et al (2018) Use of antibiotics in broiler production: global impacts and alternatives. Anim Nutr 4:170–178. https://doi.org/10.1016/j.aninut.2018.03.002

Meissonnier GM, Pinton P, Lafitte J, Cossalter AM, Gong YY, Wild CP (2008) Immunotoxicity of aflatoxin B1: impairment of the cell-mediated response to vaccine antigen and modulation of cytokine expression. Toxicol Appl Pharmacol 231:142–149

Mellor DJ (2016) Updating animal welfare thinking: moving beyond the “Five Freedoms” towards “A Life Worth Living”. Animals (Basel) 6(3):21

Midlyng PI, Grave K, Horsberg HE (2011) What has been done to minimize the use of antibacterial and antiparasitic drugs in Norwegian aquaculture? Aquac Res 42:28–34

Miele M, Evans A (2010) When foods become animals, ruminations on ethics and responsibility in care-full spaces of consumption. Ethics, Place and Environment 13(2):1–20

Mohammadagheri N, Najafi R, Najafi G (2016) Effects of dietary supplementation of organic acids and phytase on performance and intestinal histomorphology of broilers. Vet Res Forum 7:189–195

Moreno MA (2014) Opinions of Spanish pig producers on the role, the level and the risk to public health of antimicrobial use in pigs. Res Vet Sci 97:26–31

Nava GM, Attene-Ramos MS, Gaskins HR, Richards JD (2009) Molecular analysis of microbial community structure in the chicken ileum following organic acid supplementation. Vet Microbiol 137:345–353

O’Neill J (2015) Securing new drugs for future generations: the pipeline of antibiotics. Wellcome Trust, London. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20coverpdf. Accessed 22 July 2019

OIE (2013) Terrestrial Animal Health Code: Biosecurity procedures in poultry production. http://www.oie.int/indexphp?id=169&L=0&htmfile=chapitre_biosecu_poul_productionhtm. Accessed 22 July 2019

OIE (2014) Terrestrial Animal Health Code: General recommendations on disinfection and disinsection. http://www.oie.int/indexphp?id=169&L=0&htmfile=chapitre_disinfec_disinsecthtm. Accessed 22 July 2019

OIE (2015) Report of the meeting of the OIE ad hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals. http://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Anti microbial%20Use/AN/AHG_AMUR_Vaccines_Apr2015pdf. Accessed 22 July 2019

OIE (2018a) Report of the meeting of the OIE ad hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals. http://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Anti microbial%20Use/AN/AHG_AMUR_Vaccines_ruminants_May2018pdf. Accessed 22 July 2019

OIE (2018b) Terrestrial Animal Health Code: Vaccination. http://www.oie.int/indexphp?id=169&L=0&htmfile=chapitre_vaccinationhtm. Accessed 22 July 2019

OIE (2019) Terrestrial Animal Health Code: Animal welfare. http://www.oie.int/indexphp?id=169&L=0&htmfile=titre_17htm. Accessed 22 July 2019
Park JY, Moon BY, Park JW, Thornton JA, Park YH, Seo KS (2017) Genetic engineering of a temperate phage-based delivery system for CRISPR/Cas9 antimicrobials against Staphylococcus aureus. Sci Rep 7:44929. https://doi.org/10.1038/srep44929

Pierron A, Alassane-Kpembi I, Oswald IP (2016) Impact of mycotoxin on immune response and consequences for pig health. Anim Nutr (Zhongguo xu mu shou yi xue hui) 2(2):63–68

Postma M, Backhans L, Collineau L, Loesken S, Sjölund M, Belloc C, Emanuelson U, Grosse Beilage E, Stärk KDC, Dewulf J (2016) The biosecurity status and its associations with production and management characteristics in farrow-to-finish pig herds. Animal 10:478–489

Raith J, Trauffer M, Firth CL, Lebl K, Schleicher C, Köfer J (2016) Influence of porcine circovirus type 2 vaccination on the level of porcine circovirus type 2 vaccination on the level of antimicrobial consumption on 65 Austrian pig farms. Vet Rec 178:504

Rasschaert G, Michiels J, Tagliabue M, Missotten J, De Smet S, Heyndrickx M (2016) Effect of Organic Acids on Salmonella Shedding and Colonization in Pigs on a Farm with High Salmonella Prevalence. J Food Prot 79:51–55

Ratna A, Arora SK (2018) Immunomodulators as therapeutic option in parasitic infections. J Bacteriol Vaccin Res 1(1):1002

Rieckmann K, Pendzialek SM, Vahlenkamp T, Baums CG (2020) A critical review speculating on the protective efficacies of autogenous Streptococcus suis bacterins as used in Europe. Porcine Health Management 6:12

Roerink F, Morgan CL, Knetter SM, Passat MH, Archibald AL, Ait-Ali T, Strait EL (2018) A novel inactivated vaccine against Lawsonia intracellularis induces rapid induction of humoral immunity, reduction of bacterial shedding and provides robust gut barrier function. Vaccine 36(11):1500–1508

Rojo-Gimeno C, Postma M, Dewulf J, Hogevleen H, Lauwers L, Wauters E (2016) Farm-economic analysis of reducing antimicrobial use whilst adopting improved management strategies on farrow-to-finish pig farms. Prev Vet Med 129:74–87

RUMA (2016) RUMA Guidelines: Responsible use of vaccines and vaccinations in farm animal production. https://www.ruma.org.uk/wp-content/uploads/2014/09/farm-vaccine-long.pdf

Rushton J (2015) Anti-microbial use in animals: how to assess the trade-offs. Zoonoses Public Health 62(Suppl 1):10–21

SAPHIR (2019) EC-CORDIS: Strengthening animal production and health through the immune response: Fact sheet. https://cordis.europa.eu/project/rcn/193183/factsheet/en. Accessed 22 July 2019

Sasaki Y, Sekiguchi S, Uemura R, Sueyoshi M (2015) The effect of depopulation and restocking on reproductive and growth performances on Japanese commercial pig farms. J Vet Med Sci 78:333–335

Scherpenzeel CGM, Santman-Berends IMGA, Lam TGJM (2017) Veterinarians’ attitudes toward antimicrobial use and selective dry cow treatment in the Netherlands. J Dairy Sci 101:1–10

Sharma C, Rokana N, Chandra M, Singh BP, Gulhane RD, Singh Gill JP, Pallab R, Puneja AK, Panwar H (2018) Antimicrobial resistance: its surveillance, impact, and alternative management strategies in dairy animals. Front Vet Sci 08:fvets.2017.00237

Smith R, Coast J (2013) The true cost of antimicrobial resistance. BMJ 346:f1493

Swinkels JM, Hikens A, Zoch-Golob V, Krömker V, Buddiger J, Jansen J, Lam TGJM (2015) Social influences on the duration of antibiotic treatment of clinical mastitis in dairy cows. J Dairy Sci 98:2369–2380

Trujillo-Barrera A, Penning JME, Hofenk D (2016) Understanding producers’ motives for adopting sustainable practises: the role of expected rewards, risk perception and risk tolerance. Eur Rev Agric Econ 43:359–382

van Rennings L, von Munchhausen C, Oittlie H, Hartmann M, Merle R, Honscha W, Kasbohrer A, Kreienbrock L (2015) Cross-sectional study on antibiotic usage in pigs in Germany. PLoS One 10: e0119114

Vapnek J, Chapman M (2010) for the Development Law service Food and Agriculture Organization of the United Nations Legal Office: Legislative and regulatory options for animal welfare. Legislative Study 104. http://www.fao.org/3/i1907e/i1907e00.pdf. Accessed 22 July 2019

Visschers VHM, Backhans A, Collineau L, Loesken S, Nielsen EO, Postma M, Belloc C, Dewulf J, Emanuelson U, Grosse Beilage E, Siegrist M, Sjölund M, Stärk KDC (2016) A comparison of pig farmers’ and veterinarians’ perceptions and intentions to reduce antimicrobial usage in six European countries. Zoonoses Public Health 63:534–544

Welfare Quality (2009) Aims and objectives Welfare Quality project. www.welfarequality.net. Accessed 22 July 2019