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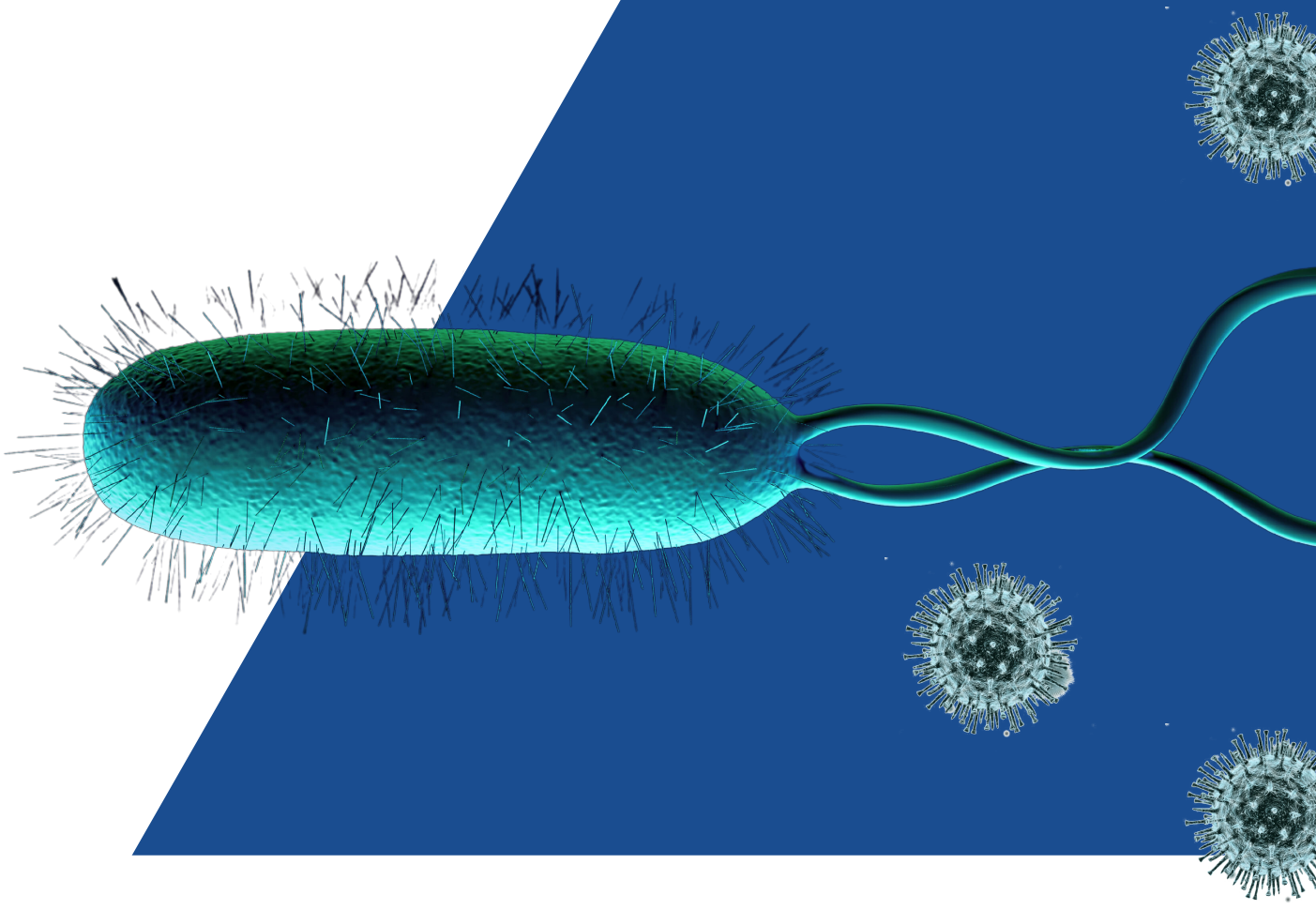
Autogenous Vaccines & Sera



MANUAL OF AUTOGENOUS VACCINES

2023

Manual of Autogenous Vaccines (AV)

Edited by European Manufacturers of Autogenous Vaccines & Sera (EMAV)

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Introduction/Foreword

Klaus-Peter Behr
Chairman European Manufacturers of Autogenous Vaccines and Sera

The legal framework for the manufacturing as well as the scope of application of autogenous vaccines was harmonised for the first time in the European Community with Regulation (EU) 2019/6, being applicable from January 28th, 2022.

Previously, these products were anchored in European law only by their definition, which served solely to exclude them from the scope of Directive (EU) 2001/82 (Article 3 No 1 (b): "*inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of that holding in the same locality*").

Until now, it was left to the member states to regulate the manufacturing and use of such products in their national legislation under the Community definition (inactivated, only for use in the same herd and in the same geographical location from which the isolate originates).

Under the new harmonised regulation, such products can now also be used throughout the EU in animals kept in the same epidemiological unit or even in a different location from the place of isolate collection, providing an epidemiological link is confirmed (Regulation (EU) 2019/6, Article 2 Nr 3: "... *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*").

Article 106 (5) of Regulation (EU) 2019/6 restricts autogenous vaccines to "*only be used in exceptional circumstances, in accordance with a veterinary prescription, and if no immunological veterinary medicinal product is authorised for the target animal species and the indication*".

The products in question are tailor-made for the individual case, they are not subject to efficacy testing nor are they subject to governmental batch release in most EU member states. The expansion of their spatial application horizon is therefore associated with risks. This is why the legislator is now simultaneously prescribing a GMP procedure for their manufacturing, although the GMP criteria are to be eased in comparison to industrially manufactured vaccines in order to ensure the market availability of these vaccines.

Recital 70 of Regulation (EU) 2019/6 explicitly states: "*although inactivated immunological veterinary medicinal products referred to in article 2(3) should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products. That would preserve their quality without hindering their manufacturing and availability*".

This recital points out a special path which requires a separate GMP criteria catalogue for these products ("detailed guidelines of good manufacturing practice ... for those products") as a stand-alone document. Proposals for such a GMP guideline have been published by EMAV - European Manufacturers of Autogenous Vaccines and Sera: https://www.emav.be/position-papers.

Together with IABS - International Alliance for Biological Standardisation - and an international panel of experts, recommendations for the implementation of the new EU GMP standard were also formulated and published https://authors.elsevier.com/sd/article/S1045-1056(22)00003-3.

Why is such an exemption created in European law at all? There are a number of reasons, mainly in the area of animal welfare and the reduction of the use of antibiotically effective medicines.

From the point of view of animal welfare, it seems to make sense to carry out vaccination prophylaxis against all disease agents by which animals are threatened. Providing no industrially manufactured and licensed vaccines are available, this should also be possible in future with the help of vaccines manufactured individually and for each case.

In order to be able to fill the new legal situation with life, the editors and the authors would like to
- discuss the newly introduced terms of epidemiological unit and epidemiological link,
- discuss application contexts for different animal species and directions of use, and
- present pathogen-related examples of use, which can only be examples due to the current vaccine approval situation in the respective member states.

As soon as the new GMP manufacturing rules for autogenous vaccines become legally binding, these products will only be produced within the EU by manufacturers who then hold the relevant GMP certificate. Such products can then be supplied directly to veterinarians in all member states by manufacturers holding the new EU GMP certificate. These vaccines are available only by prescription and it will be up to the prescribing veterinarian to assess whether animals belong to an epidemiological unit

or to confirm the epidemiological link. It is precisely for this purpose that this manual is also intended to provide assessment guidance.

We were able to recruit authors from various universities, other experts and also authors from the circle of EMAV member companies to contribute to this handbook. In Chapters 1 and 3 the contributions are identified by name; Chapter 2 was written by a collective of authors, including employees from various companies active in the manufacturing of autogenous vaccines. All contributions in this handbook reflect the views of the respective authors. This manual should therefore not be regarded as the official position of EMAV - European Manufacturers of Autogenous Vaccines and Sera.

1. The Importance of Autogenous Vaccines (AV) for a Modern Vaccine Portfolio and General Aspects of their Use

1.1. General aspects of a vaccine portfolio and AV

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Significant progress has been made in both, human and veterinary medicine through the use of vaccination and it is undisputed that the importance of immunoprophylaxis will continue to increase. The eradication of smallpox in humans and rinderpest in cattle are examples of disease control measures that would not have been possible without vaccination. The progress in rabies control in Europe, the eradication of Aujeszky's disease in pigs in many countries, the reduction of BHV-1 infections in cattle, the significant reduction of salmonella infections in poultry with a positive effect on human salmonellosis and the successful control of bluetongue outbreaks also speak for the value of vaccination.

In recent years, the reduction of antibiotic use in animals has become an important goal of immunoprophylaxis. The increase in bacterial resistance to antibiotics is seen as a worldwide health problem (Klein et al., 2018). The EU adopted an action plan as early as 2011 and many other positions and definitions on this topic in the period thereafter. The EU Regulation 2019/6 on Veterinary Medicinal Products contains clear provisions in the sense of controlled use and reduction of use (Article 107). In addition, Article 57 formulates rules for data collection. For years, national legislation has been geared towards responsible use with the aim of significantly reducing the amount of antibiotics used in animals. To this end, the evaluation report of the German Federal Ministry of Food and Agriculture of 2019, for example, provides an overview of the status achieved in Germany in reducing the use of antibiotics in fattening animals (calves, cattle, piglets, pigs, turkeys, chickens). From 2011 to 2020, the quantities sold in Germany were reduced by a total of 1,005 t (= 58.9%). In detail, this concerned for example:

Tetracyclines	416.7	t =	73.8% reduction
Penicillins	250.3	t =	47.4%
Sulphonamides	119.6	t =	64.7%
Trimethoprim	21	t =	70.3%
Macrolides	112.3	t =	64.9%
Fluoroquinolones	1.8	t =	22.3%
Cephalosporines 3rd generation	0.2	t =	52.2%
Cephalosporines 4th generation	0.2	t =	79.7%
Polypeptides	67.2	t =	52.8% reduction

(Gefeller et al., 2021).

On EU level, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched from EMA in 2009. The 10th ESVAC report 2018 summarised: “For the 25 countries which provided sales data for all years between 2011 and 2018, an overall decline in sales (mg/PCU) of 34.65% was observed.”
In detail the following reductions where achieved:

3rd and 4th generation Cephalosporines	– 24.0%
Polymyxins	– 69.8%
Fluoroquinolones	– 4.2%
Other Quinolones	– 74.4%

(EMA/24039/2020).

The lack of antiviral drugs for many indications also underlines the importance of vaccination. The same applies to certain therapy-resistant, chronic infectious diseases (e.g. in dogs, horses and rabbits) for which a therapeutic success can be achieved through the use of autogenous vaccines.

The vaccine portfolio for veterinary medicines was significantly expanded and new solutions regarding protective antigens, adjuvants and manufacturing processes have been and are being developed. In this respect, questions of vaccine availability and the cost-effectiveness of their development, production and application play an important role. In the following, the prerequisites and conditions for the use of autogenous vaccines (AV) will be examined and their relevance for the current and future vaccine portfolio will be highlighted.

The veterinary vaccine industry and market

The latest available report of the International Federation of Animal Health (IFA) estimates, as of 2013, a worldwide annual turnover of $23 billion for veterinary medicines, 26% of which was accounted for by biologicals (www.bft-online.de /22.05.2020).

The actual figures of the world market for veterinary medicines fluctuated in various publications as having a volume of between $12.2 and about $33.6 billion (Peters, 2018 - Animal Health Report; www.healthforanimals.org). One source quotes about $7 billion in sales of vaccines, with an expected increase to about $9 billion by 2024 (www.healthforanimals.org), another expects sales to grow up to $11.3 billion by 2025 (www.marketsandmarkets.com/ 22.05.2020) Other evaluations assume vaccine sales of $6.5 to 12.1 billion, which should increase to $20.6 billion in the 2020s (Peters, 2018). The positive market expectations for vaccines are consistent.

The European market is the second largest veterinary pharmaceutical market in the

world after North America, accounting for about 1/3 of global sales. In 2021, according to data from Animalhealth-Europe, the European veterinary drug market had a volume of about € 7.4 billion, of which 32.2% accounted for vaccines. The share of vaccines has increased in recent years, whereas the share of antibiotics has fallen.

The market shares are:

32.2 %	Vaccines
28.9 %	Parasitics
11.2 %	Antimicrobials
27.7 %	Other.

The distribution among the animal groups is as follows:

42.4 %	Pets
29.7 %	Livestock (cattle, pigs, sheep)
10.9 %	Poultry and avian
2.8 %	Horses
1.8 %	Aquatics (non-pet)
12.4 %	Others (www.animalhealtheurope.eu).

This data covers about 90% of the European Market (Animalhealth-Europe) represents12 leading manufacturers and 16 national associations in 19 countries).

In 2021, the veterinary pharmaceutical industry in Germany generated sales of €900 million. Vaccines contributed 229 million €, representing 28% of sales. In 2020 sales were 878 million € and the share of biologicals was 237 million € (www.bft-online.de).

Worldwide, concentration within the pharmaceutical industry has increased significantly, with around 70% of sales being generated by the top five companies Zoetis, Merck Animal Health, Elanco, Sanofi and Bayer Animal Health based on revenue in 2017 (Peters, 2018). Zoetis has held the top position for years with annual sales of $6.3 billion in 2019 (www.zoetis.com /24.11.2020). The next two in the ranking are Elanco who has established itself after the takeovers of Novartis Animal Health and Bayer Animal Health followed by Boehringer Ingelheim after the takeover of Merial (Sanofi). However, this also has consequences with regard to the concentration of development budgets primarily on products for global use, with which it is possible to refinance the not inconsiderable development costs.

Market data on AV are hardly available. For Germany, the Paul-Ehrlich-Institute (Federal Institute for Vaccines and Biomedicines) publishes annual data on the number of manufacturers, the number of batches and the number of vaccine doses produced. In 2019, 18 AV manufacturers were registered, producing 16,681 batches with a total

of more than 218 million vaccine doses. They were divided among the animal species as follows:

Poultry & ornamental birds	4,126	batches	with 184.43 million doses
Fish	117	batches	more than 17.6 million doses
Pig	5,586	batches	more than 15.2 million doses
Ruminants	3,606	batches	807,085 doses
Dog, cat, mink	2,477	batches	134,567 doses
Zoo animals	50	batches	78,692 doses
Rabbit, pets/small animals	79	batches	26,967 doses
Horse	640	batches	7,992 doses

(www.pei.de/ 19.01.2021).

Market Drivers

The increasing demand for veterinary vaccines is globally determined by the following aspects, which naturally have different territorial and national focuses:
- Rising demand for food
- Rising number of pets and companion animals
- One-Health approach, combating zoonoses
- Emerging and re-emerging diseases and zoonoses threat
- Increasing risks of infection from global movement of people, animals, food and products
- Reduction of the use of antibiotics in animals to influence the resistance situation.

Vaccine technologies

The development of new vaccines is often a very long process in which time spans of many years can elapse between primary scientific and research results, the formulation of new concepts and eventually, the actual availability of the licensed products on the market.

Prior to the introduction of molecular biological and genetic engineering methods, vaccines could be divided into inactivated (killed vaccines) and live vaccines. Classical inactivated vaccines are produced from complete, virulent bacterial cells or virus particles. In the case of toxoid and split or subunit vaccines, the virulent strains of pathogens are cultivated, the toxins are separated from the culture material or the antigens are obtained as a split or a subunit of the pathogen (e.g. fimbriae from coliform bacteria or haemagglutinins from influenza viruses). Pathogens contained in such inactivated vaccines are not capable of reproduction. The classical live vaccines are produced from xenogenic (heterologous) or attenuated strains.

These conventional concepts certainly lead to effective products, however, modern methods have significantly expanded the possibilities. Examples of vaccines that are approved for the European market using such new technology are:

- Recombinant subunit vaccines - e.g. against PCV 2, porcine parvovirosis and oedema disease (expression systems e.g. coli bacteria or baculoviruses);
- Live vaccines with genetically modified vaccine strains - e.g. against rabies of foxes;
- Vector vaccines - e.g. based on canary pox, myxomatosis or turkey herpes viruses, as well as chimeric BVD (against swine fever), Flaviviruses (against West Nile virus) and PCV 1 (against PCV 2) viruses;
- DNA vaccine against SAV infections (pancreatic disease) in salmon (first approval of a DNA vaccine in the EU in 2017).

Research is also carried out on the expression of antigens in plant cells and the synthetic production of vaccine antigens (peptides and glycans).

A completely new method is used in connection with the development of Covid 19-vaccines for humans – the mRNA vaccine. In veterinary medicine, there are no examples of such products yet.

In addition, there are of course developments in adjuvants, application systems and the development of programmes for animal disease control and animal health management.

The improved combination of laboratory diagnostics and immunoprophylaxis is a driving force for a broader use of vaccines. Laboratory diagnostics must be developed not only to determine optimal vaccination timing, but also to verify the success of vaccination. The DIVA (differentiating infected from vaccinated animals) principle can overcome the issue between serological monitoring and vaccination programmes.

These examples illustrate that modern methods of vaccine development have led to significant advances in vaccine availability and will largely determine future developments. However, these developments involve considerable expenditure and will therefore only be applied to products that are expected to have a certain market size. This means that these methods will not be able to cover the entire vaccine portfolio required in the foreseeable future.

From the technological point of view AV are classical inactivated, adjuvanted vaccines.

Availability of vaccines

The availability of vaccines for a wide range of indications is indisputably a prerequisite for further progress in animal disease control and animal health management. However, in addition to the clearly positive trend in the development and approval of new vaccines, problems cannot be overlooked.

One of these is the increasing focus on the development of products suitable for larger, preferably global, market. This is due to the size and international positioning of pharmaceutical companies as well as the high regulatory requirements for the production of vaccines and the testing of safety and efficacy as well as pharmacovigilance. With regard to European developers and manufacturers, this means a clear focus on the Centralised Procedure of registration through the EMA (European Medicines Agency). Problems have already arisen and are continuing to develop with regard to the vaccine portfolios for

- animal species that are less common and kept in smaller numbers (minor species)
- less frequent indications (minor use) and
- limited markets.

Under the term MUMS (minor use / minor species) / limited markets, efforts have been underway for years to counteract these portfolio bottlenecks by reducing approval requirements. In the USA, this situation was already taken into account in 2004 with the enactment of the so-called MUMS act. The definitions applicable in the EU are described in a guideline (EMA/CVMP/388694/2014.Rev 2 Corr.).

In the EU, the problem of the availability of a sufficient vaccine portfolio is at least recognised. In the “EU Medicines Agencies Network Strategy to 2020” (EMA/MB/151414/2015) adopted in 2015, the “... increased availability of veterinary medicines...” was formulated as a priority task.

In 2016, a “Joint EMA/HMA Veterinary Vaccines Availability Action Plan” (EMA/239617/2016) was adopted. This plan identifies the promotion of mutual recognition of national vaccine authorisations (MRP), the authorisation of MUMS products and autogenous vaccines as instruments. A Steering Group continues to work on the implementation of this plan (EMA/565300/2017).

In the Comments received on „Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU (EMA/CVMP/461776/2017) autogenous vaccines are defined as “… significant tools in the prevention of antimicrobial resistance where gaps of authorisations of vaccines still exist and no registered vaccine is available.” (EMA/644209/2020).
The European medicines agencies network strategy 2025 (EMA/85501/2020) lays a

strategic focus on “3.1. Availability and accessibility of medicines” and runs under strategic goals “the availability of medicines to protect the health of European citizens and animals”. The implementation of the Regulation (EU) 2019/6 on 28 January 2022 superseded EMA’s former MUMS / limited market policy and is the special focus of this document with regard to veterinary medicine.

Legal Framework

The former EU Directive 2001/82/EC on Veterinary Medicinal Products did not regulate AV and thus left it to the member states to make stipulations. Nevertheless, there were: “Recommendations for the manufacture, control and use of inactivated autogenous veterinary vaccines within EEA” (EMA/CMDv/452656/2016/REC-002-01).

Regulation (EU) No. 2019/6 on Veterinary Medicinal Products changes this situation fundamentally. In Article 2 (3) the AV are defined 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”.

The validity of certain articles of this Regulation is then expressly extended to the AV (see Chapter 2.1). Article 106 (5) is also relevant, as it permits the use of AV: “...in accordance with a veterinary prescription, and if no immunological veterinary medicinal product is authorised for the target species and the indication.”

For the first time, manufacturing under the rules of Good Manufacturing Practice (GMP) becomes binding for AV. However, the need for specific regulations is recognised:

“(70) Although inactivated immunological veterinary products referred to in Article 2(3) should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products.”

According to Article 159, GMP certificates for AV are only required after “...application of the implementing acts laying down specific measures on good manufacturing practice...”.

These provisions of the Regulation on Veterinary Medicinal Products clearly show the importance that is now being attributed to GMP certificates. At the same time, they contain the most important legal framework for the production and use of the AV.

In 2021, the EMAV prepared a proposal for an **EU-GMP-Annex for Autogenous Vaccines** (https://www.emav.be/position-papers).

Conclusions

Vaccination is one of the most effective methods in the control of animal diseases and zoonoses and in animal health management. Amongst other factors, its increasing relevance is owed to the task of reducing the use of antibiotics. This requires a broad portfolio of vaccines, in which AV play an indispensable role.

Three main areas can be formulated for the use of vaccines in animals:

- the control of animal diseases
- the one-health approach with the main objective of combating zoonoses
- animal health management including reduced use of antibiotics.

The development and approval of commercial vaccines has made considerable progress in recent years and new technologies have been successfully introduced. However, in conjunction with the high development costs, the increased demands on safety and efficacy, as well as the requirements of Good Manufacturing Practice with regard to manufacturing processes, the main focus is given on vaccines with large international market potential. The concentration of vaccine development and production in large, international pharmaceutical companies accelerates this process. For this reason, vaccines are not being developed to the necessary extent for certain animal species kept in smaller numbers, nor for rarer indications in other animal species. The discussions about minor species, minor use and minor markets that have been on-going for years highlight this problem.

The production of AV is part of a solution to be able to provide all animal species under veterinary care with the necessary vaccines. In addition, AV are suitable for bridging the periods until registrations of new products are accomplished and for meeting stock-specific pathogen spectra.

In contrast to the Veterinary Medicinal Products Directive 2001/82/EC, the new Regulation (EU) 2019/6 on Veterinary Medicinal Products includes AV.

Autogenous vaccines have a firm place in the vaccines portfolio which must be maintained and further expanded.

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1.2 Basic Epidemiological Aspects

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A General Epidemiological Concepts for Autogenous Vaccination

Epidemiology is concerned with the study of the distribution of diseases, physiological variables and disease consequences in populations and parts thereof, as well as with the factors that influence this distribution. By identifying the causes of disease, it creates the basis for the development, implementation and evaluation of targeted preventive measures.

This general definition also applies for measures related to (autogenous) vaccination. Here the events of interest are the animal disease or more precisely the infection with a specified disease agent, as well as the status of the animal's susceptibility against this pathogen of interest, and the factors, which drive these events.

Hence, the general goal of epidemiology is to study the distribution of a disease or susceptibility status within a population (descriptive epidemiology) as well as the drivers of this distribution (analytical epidemiology). Therefore, it is crucial to set up some definitions of epidemiology first.

In the context of (autogenous) vaccines following the classical concept of epidemiology, we therefore want to first define the populations under study and the susceptibility status as the target information of interest.

A 1 Population under Study

Generally, epidemiology is defined as population medicine, i.e. the study of medical events in a group of units of interest, which often is named as population under study. In veterinary medicine, these units are generally animals. However, a group of animals,

e.g. animals on a farm may act as a unit of interest as well. To distinguish between these views in veterinary medicine they are identified by using "individual level" or "herd level" as scientific terms.

An entire group of units of interest forms a population. This group usually is referred to as the population at risk, the target, the reference or the basic population or the totality. It indicates the part of the population for which the result of an epidemiological investigation should be valid. For example, the entire animal population of a country, animals of a certain breed or production type can be regarded as a target population.

In the following we want to distinguish the views of a population with regards to autogenous vaccines. On one hand, we want to investigate the **entire population level**, i.e. totality of all animals of a country or a district. This is mainly of interest for reporting on the animal population as its whole. On the other hand, each farm itself may represent a target. This usually is the focus of veterinary action and may be addressed as the **population on farm-level**.

If a target population empirically has to be investigated as such, e.g. by determining its disease or its susceptibility status on a given reference date, it is necessary to record the status for all members of this population in order to determine the proportion of those affected.

It is obvious that this approach is practicable for small populations only. Therefore, a so-called **census**, total or full survey of a target population can only be carried out in very few cases. Such a procedure is conceivable if, for example, the target population can be limited spatially. This shows, however, that such censuses have organizational, technical and, above all, financial limits. A full census therefore must be viewed as an exception of an epidemiological investigation.

The standard form of an epidemiological investigation is the sampling of a group of individuals. The investigation, study or **sample population** is the subpopulation on which an actual investigation is carried out.

A wide variety of techniques are conceivable for choosing a study population. The selected study group should be as representative as possible of the target, i.e., it should structurally match the target population. Note, that the sample size of an investigation is not a matter of representativeness. But the practical feasibility also plays a role in the acquisition of samples. Basically, one can divide the procedure for determining samples into three different principles. A distinction is made between

(1) the random selection of individuals,
(2) the selection after prior assessment, e.g. by means of veterinary inspection, and

(3) by chance, i.e. as a convenience sample (with generally no control of the selection process).

The degree of representativeness is higher the closer the entire selection process is to the random principle. For more details in special techniques please see Cochran, 1977, Kreienbrock, 1993, Dohoo et al., 2009, Kauermann & Küchenhoff, 2011.

When investigating autogenous vaccines these definitions are supported by an additional term, "**the epidemiological unit**". By means of the EU-Regulation 2016/429, Article 4 No. 39 this is "a group of animals with the same likelihood of exposure to a disease agent".

The Article 2(3) of the EU-Regulation 2019/6 is decisive for the administration of autogenous vaccines. The use is allowed "… 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."

In the light of the definition above the "epidemiological unit" is a specific characterisation of a population under study, which restricts the population. From the perspective of sampling theory, we call this restriction a **stratification**, i.e. the population is separated into strata, classes or sub-groups itself.

In classical sampling theory the stratification usually has two reasons. First, stratification serves to provide clarity and structure of a population, but also leads to simplifications in the sampling procedures. And second, stratification in classes with homogeneity within and heterogeneity between the groups helps to narrow the entire variance of results, if an overarching interpretation for the entire population is crucial.

This second reason is helpful for the definition and interpretation of the "epidemiological unit" as well, because the definition is linked to "the likelihood of exposure to a disease agent". In other words, the so-called stratification variable of the entire population of animals is related to the exposure risk of a pathogen, which itself is causing the risk of infection. As the risks themselves are vague they have to be defined within each application separately.

However, in any case it must therefore be checked whether the animals belong to an epidemiological unit or whether there is an epidemiological link between these units. Therefore, it is necessary to have a closer look into the susceptibility status as a main reason for (autogenous) vaccination.

In the setting of (autogenous) vaccination usually a basic cause-effect model (see Figure 1) may be used.

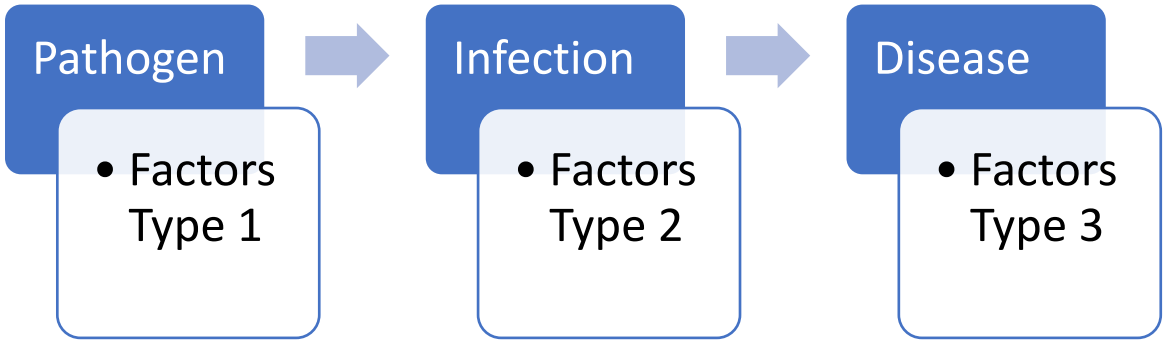

Figure 1: Basic cause-effect model of infection and accompanying factors

The general idea that an animal, which is exposed to a pathogen may become infected and from this a disease may develop accompanied by a series of factors, that drive the development of this process.

As proposed by Figure 1, three types of drivers of the infection can be distinguished:

factors type 1: Within a given population (e.g. farm) a number of factors exist, which drive the occurrence of a disease agent. Usually, these factors are related to classical hygiene measures, like internal and external biosecurity, general farm maintenance and others.

factors type 2: If an animal is exposed to a pathogen, the chance of becoming infected exists. This opportunity is mainly influenced by individual factors, which directly and indirectly are related to the animal's individual susceptibility status. The most important driver here is the vaccination, but other factors like immunity from previous infections, breed, feeding and other aspects of preventive farm maintenance are popular examples of these factors.

factors type 3: The outcome whether or not the infection leads to disease is also driven by external management factors, like quality of feed and others (e.g. ectoparasitic burden, extreme crowding), as these influence the individual nutrition and health status. And, the mode of transmission of

the disease agent can influence this outcome, as the infectious dose may not have been sufficient to cause disease even though an infection took place (see below).

Linking this view to the definition of an epidemiological unit, “the group with the same likelihood of exposure…” is directly associated to the type 1 factors. In terms of epidemiology, i.e. to identify drivers, these usually are associated to the occurrence of the pathogen within an entire target population of interest.

It is obvious, that the animal species and in particular the production type is crucial for this relationship between factors and the pathogen occurrence. The same is true for the pathogen under study itself, which usually has particular infection and transmission routes. So, in the light of (autogenous) vaccination, a generic concept to define an epidemiologic unit including a structural process seems appropriate.

A 3 Generic Concept to Define an Epidemiological Unit

Based on the basic model of infection (see Figure 1), a general framework of defining an epidemiologic unit is proposed. For this, a four-step process seems essential (Figure 2).

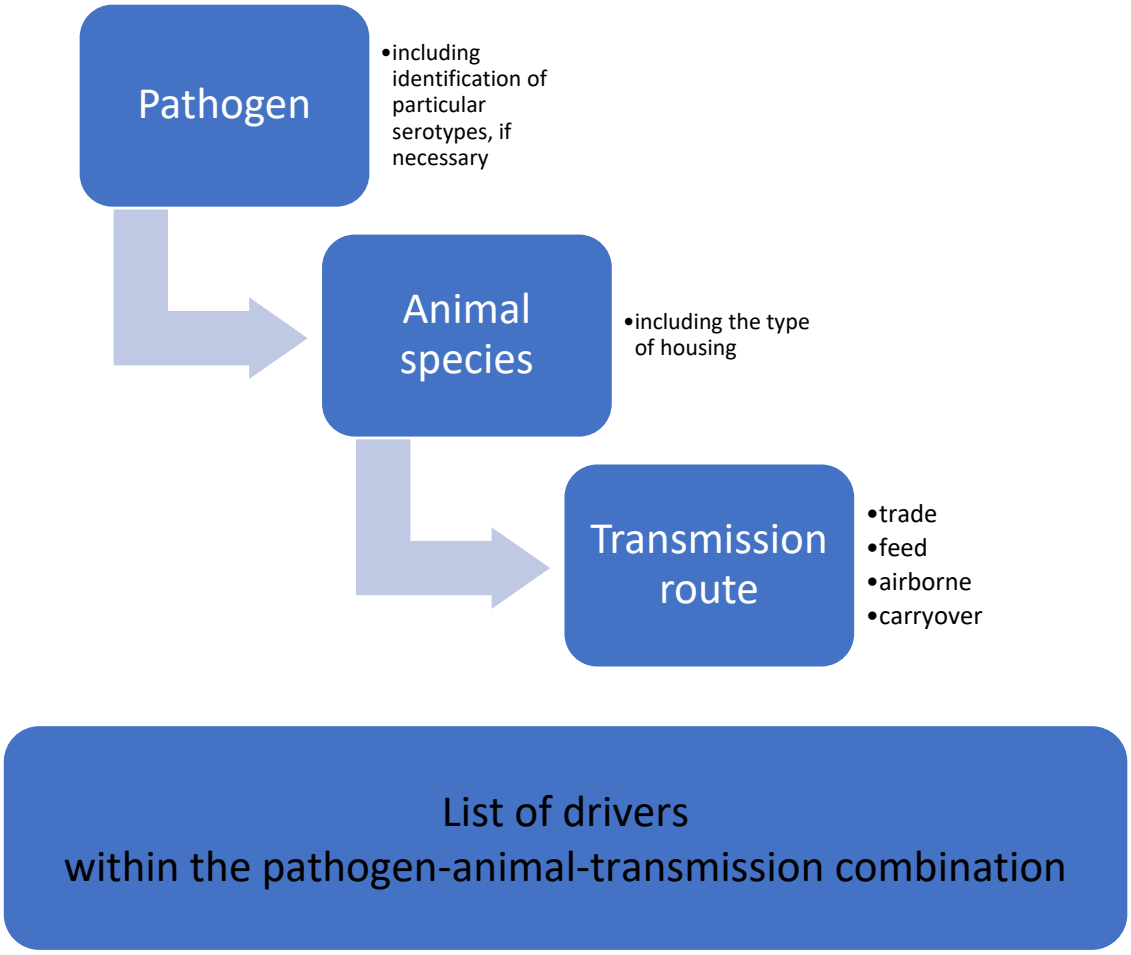

Figure 2: Framework to define an epidemiological unit for the administration of (autogenous) vaccination

Within the first three steps, the pathogen, the animal species (including its form of housing) and the transmission routes have to be addressed. This combination is crucial to start the definition process of a possible stratification into epidemiological units.

Based on this combination, a list of (important) drivers for the occurrence of pathogens have to be discussed. The list as such has to be formulated for each combination individually under the responsibility of the consulting veterinarian. It has to be pointed out that on one hand, all possible drivers on the occurrence of pathogens have to be taken into account. On the other hand, if the number of drivers increase the number of epidemiological units may increase exponentially, which restricts the practical usability within a target population.

Despite the drivers shown in Figure 2, which we consider useful to define the epidemiological unit, the epidemiological link connecting different epidemiological units warrants some further thoughts. While the epidemiological unit is a spatially rather restricted concept, the epidemiological link can broaden the epidemiological unit

spatially and temporally. As this, by nature, is often opposing the basic definition of the epidemiological unit, it is challenging for the veterinarian to identify this epidemiological link.

Such a link can be established in facilities with an integrated production chain, even if e.g. weaning pigs and the fattening deck are kept in separate holdings. But such a connection can also make sense when the latter are sold to another holding. In the pig and poultry industry stable trading connections between holdings also fulfil the epidemiological link, i.e. when suckling pigs are vaccinated with an autogenous vaccine prepared from an isolate of the fattening deck where these animals will be housed in some weeks. Likewise, young poultry can be vaccinated with an autogenous vaccine made from a pathogen that is causing problem in the holding, where these animals become laying hens or broilers. This link, however, is only valid, when the animals definitely end up in the holding from where the pathogen was isolated and served as basis for the autogenous vaccine. The veterinarian in charge, who knows the local circumstances and production chains best, is responsible for judging whether or not the epidemiological link justifies an autogenous vaccine.

To demonstrate this process of identifying drivers, which define an epidemiological unit as well as the link connecting different units, examples are given in Chapter 2. But the main message is: to use an autogenous vaccine, the epidemiological unit has to be determined separately for each situation and the concept above may prove helpful for the veterinarian at the site.

B Practical Concepts to Define an "Epidemiological Unit" by Animal Species

Production and administration of autogenous vaccines varies considerably among animal species. For example, roughly 200 million doses are produced annually in Germany, with a majority (>75%) for use in poultry and other bird species. About 10% were produced both for swine and fish with only about 1% for the cattle industry. The remaining doses were manufactured for companion animals, mink, rabbits, horses and zoo animals, altogether accounting for less than 1% of doses. Nevertheless, through a higher species diversity and less animals per epidemiological unit (and thus a smaller production scale), the last group represents about one-sixth of all batches produced (Paul-Ehrlich-Institute, 2020).

B 1 Cattle (i.e. dairy and beef)

There is a large portfolio of licenced, commercial vaccines available which leave few gaps to be filled by autogenous vaccines. Another fact in the cattle industry which is hampering a more frequent use of autogenous vaccines is the early movement of

calves into new holdings. This is true at least for Germany and various other countries/regions.

Calves are usually separated from their mothers the day after their birth when colostrum feeding has taken place. They are then kept in igloos or other separate housings or in small groups separated from adult animals. In most cases they are sold within the first 14 days of life and moved onto another farm, where these young animals are kept together in newly assembled groups mostly for fattening purposes. Usually, these animals cannot be vaccinated against specific disease agents that might be prevalent in the new environment as this should have been done in the previous stable. However, the epidemiological link allows to already vaccinate calves - before they are moved - against a pathogen known to be present in the new environment if this calf trade is well established and justifies this epidemiological link. So, in contrast to the highly organised production chains in swine and poultry industry (see below), the situation in cattle is more diverse when it comes to epidemiological unit and mixing of animals of different origin.

Nevertheless, some clinical syndromes may call for autogenous vaccination when the pathogen is not (or not sufficiently) covered by a licensed vaccine. These include diarrhoea in calves (*E. coli* and others), but also diseases in adult cows, e.g. mastitis in cases where too many individuals are affected and antibiotic treatment is no option (*Klebsiella* spp., *E. coli*), keratoconjunctivitis (*Moraxella* spp.), or abortion (various Chlamydophila species). Specific *Clostridium perfringens* strains may be formulated into autogenous vaccines in order to cover the specific toxin types. Papillomavirus, Influenza virus D and Bovine Coronavirus are further candidates for autogenous vaccines.

As for diarrhoea in calves, the question about the definition of the particular epidemiological unit is more or less solely dependent on the spatial proximity within a stable sharing feed storage, feeding system and dung removal management. In the case where young individuals are kept (singly or in groups) in a separated area on the farmyard or somewhere nearby, but outside the stable, they may be considered a separate epidemiological unit, if feeding and dung removal is separate to that of the stable. However, in practice, this is not likely to be relevant for the administration of autogenous vaccines.

B 2 Pigs (i.e. piglets / sows and weaner and fattening)

There is a need for autogenous vaccination in pig production regardless of the production type. Mainly respiratory and enteric diseases are the target of autogenous vaccination in swine production.

Although many licensed vaccines are commercially available, the list of disease agents is rather long. It includes *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp., *Pasteurella* spp., *Klebsiella* spp. *Trueperella* spp. *Mannheimia* spp. *Bordetella* spp., *Haemophilus* spp. *Mycoplasma* spp., as well as *Pseudomonas aeruginosa*, to name a few.

As with the poultry industry, a precisely timed production process is the basis for the entire sector and thus the health status of the animals is very important. Epidemiological units are in most cases rather easy to define, but have to be thoroughly checked for epidemiological links within the production chain. For example, sows are vaccinated in order to prevent disease in their offspring, as practiced with Rota A virus types which may cause devastating diarrhoea and losses in the new-born animals.

So, in the swine industry the demand is very diverse and based on the multifactorial nature of some of the symptom complexes, combined autogenous vaccines comprising a number of pathogens are not uncommon.

B 3 Sheep/Goat

The importance of autogenous vaccination in small ruminants e.g. against pseudotuberculosis, *Pasteurella* spp., *Mycoplasma ovipneumoniae* or foot rot varies considerably based on the type of holding and hygiene. Epidemiological units in sheep and goat holding are mainly to be defined by the possibility of having an epidemiological link. While flocks of both species are usually held together in one big group, such considerations are easy. Even if grazing meadows and stables could be separated, a connection has to be assumed and both parts should be considered as one epidemiological unit. Likewise, if these animals are kept indoors within one big building, besides possible or existing separations according to age or other criteria, they should be considered as one epidemiological unit.

B 4 Poultry (i.e. laying hens and broilers and turkeys)

The poultry industry is on the one hand a very well organised industry with a structured distribution net and a precisely timed production in the breeding, rearing and fattening sector. On the other hand, in particular chicken are kept in small numbers in hobby holdings and backyard farms not for commercial use, but rather for supplementing the household nutrition. The latter are simple when it comes to defining the epidemiological unit, but for the industrial production individual decisions must be made, based on the type of farm.

As proposed in our generic framework (see Figure 2), the definition of the pathogen and its transmission in poultry production is a minor topic for the definition of an

epidemiological unit. The main criteria here should include considerations of production sector, sole indoor holding with separate compartments thus minimalising epidemiological links, or access to outdoor areas.

In case of the vaccination of young animals one consideration should also be that autogenous vaccines have to be administered via a well-tolerated injection. This is important, as some of the commonly used adjuvants are prone to cause local reactions which may reduce the quality of broilers. Nevertheless, due to the short production time in poultry industry, the feedback about the positive effect of the autogenous vaccination is of great importance in order to avoid similar drawbacks in the next production round. This is also one of the reasons that in poultry industry, it is not uncommon to administer combination of autogenous vaccines. These may include different bacterial pathogens as well as bacteria and viruses.

The panel of viruses is rather small including e.g. avian reoviruses or avian adenoviruses in chicken and low pathogenic avian influenza viruses (not H5 or H7 strains). The panel of bacterial pathogens that are subject to autogenous vaccination is much larger, including mostly pathogens of the enteric or respiratory tract, e.g. *Pasteurella* spp., *Riemerella* spp., *Ornithobacterium rhinotracheale*, *Erysipelotrix rusiopathiae* or *E. coli* types to name but a few.

B 5 Fish

Aquaculture are a growing industry both with fresh and salt water fish. The production process in the fish industry is highly diversified as egg production and hatching of first live stages is strictly separated from the further growth and final fattening stages. While the first steps in fish production (in theory) can be clearly split into logical epidemiological units, the epidemiological link and the cross contamination via the jointly inhabited water is evident. The definition of the epidemiological unit thus mainly depends on the type of aquaculture, farmed species and life stage.

Salmon dominates the market on autogenous vaccines (about 50 %) followed by trout, sea bass and others. Vibriosis, Aeromoniasis, Edwardsiellosis, Pseudomoniasis, Streptococcosis, and Mycobacteriosis are the most common bacterial diseases in aquaculture. A good hygiene management is crucial not only for the fish but also for the safety of aqua farmers, field technicians, and fish processors as some of these pathogens are zoonotic.

Disease outbreaks increase production and treatment costs, an economic loss which could be reduced by the use of autogenous vaccines. Besides the treatment costs of antibiotic usage, the overall risk of promoting antibiotic resistance is pervasive. This fear will further increase the demand for autogenous vaccines over the coming years.

There are still many challenges in regard of the vaccination strategies in the fish industry and much research is going on in order to improve adjuvants and carriers or vaccine application. However, this also applies in varying degrees to all other animal species.

C Outlook: Pharmacovigilance and Control of Efficacy

Both, the general administration of registered vaccines as well as the use of autogenous vaccines is generally seen as a major pillar of disease prevention in modern animal husbandry. To improve these concepts of disease prevention several measures are useful.

Pharmacovigilance as one of these measures is not required for autogenous vaccine according to EU Regulation 2019/6, but it should be in our best interest to provide feedback to autogenous vaccine producers.

The current practice of autogenous vaccine use does neither involve a systematic evaluation of efficacy (no matter what the read out in this particular situation is) nor a feedback to the vaccine producer. The latter is usually only informed when no improvement was achieved in the health status of the vaccinated epidemiological unit. Here we want to make a statement to change this behaviour for the following reasons.

First, it is simply a matter of good veterinary and manufacturing practice to do so. The veterinarian has to document the change in frequency of the clinical picture induced by the disease agents as part of the integrated farm control. It has to be kept in mind, that autogenous vaccines by the nature of their production, cannot be tested for efficacy and safety prior to administration. Thus, such feedback, which may be called autogenous pharmacovigilance, is of utmost importance and may help to improve vaccine production in the long run.

Second, basic laboratory parameters, most of which are routinely applied for other reasons, will help to see whether or not the health status of the animals within the vaccinated epidemiological unit improved. Feed consumption, weight gain and other indirect attributes (milk or egg production) can also be very helpful in defining the (positive) effect of autogenous vaccination. In an optimal setting, parameters specific for the disease agent vaccinated against should be collected. This could involve e.g. testing for specific antibodies.

Finally, all concepts of vaccination (approved as well as autogenous) may not accomplish the permanent elimination of the disease agent. In other words, the same problem in the animal production may return and then its management could be

optimised based on the previous measurements taken, including the vaccination strategy.

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2. Examples for Production and Application of Autogenous Vaccines

2.1 Basic aspects

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Regulation (EU) 2019/6 includes autogenous vaccines in the European regulations on immunological veterinary medicinal products for the first time. Previously, differing national regulations applied. Principles are defined in Article 2 (3) of the Regulation 2019/6 (see 1.1). The rules of Good Manufacturing Practice apply to the manufacturer; the introductory part of Regulation 2019/6 explains this under Recital 70:

“Although inactivated immunological veterinary products referred to in Article 2(3) should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products. That would preserve their quality without hindering the manufacturing capability.”

The entry into force of this rule is further defined in article 159: “…shall only start to apply from the date of implementing acts laying down specific measures on good manufacturing practice…”.

For this implementation process, the EMAV has developed a position paper and presented it for discussion at a scientific meeting together with the International Alliance for Biological Standardization (www.iabs.org) in Munich in September 2021:

EMAV Proposal: EU-GMP-Annex for Autogenous Vaccines
(https://www.emav.be/position-papers).

Furthermore, Article 2 (3) states that the following articles of Regulation 2019/6 apply to autogenous vaccines:

Article 94 – Certificates of good manufacturing practice
Article 105 – Veterinary prescriptions
Article 108 – Record-keeping by owners and keepers of food-producing animals
Article 117 – Collection and disposal of waste of veterinary medicinal products
Article 120 – Advertising of veterinary medicinal products subject to veterinary prescription
Article 123 – Controls
Article 134 – Prohibiting of supply of veterinary medicinal products.

It is the responsibility of manufacturers and prescribing veterinarians, as well as animal owners, to consider these conditions for the production and use of autogenous vaccines. An important role is played by diagnosticians, who must supply the correct strains for the production of AVs.

In addition to the manufacturing process and the application, the selection of the pathogen strains plays a decisive role for the effectiveness of autogenous vaccines. Therefore, the greatest importance must be attached to this diagnostic aspect in every case. The microbiological/virological examination must be carried out on the basis of the preliminary clinical report and, if necessary or available, pathological-anatomical findings. The selection of the diagnostic material already lays the foundation for the later successful selection of suitable strains. For the diagnostic procedure, the general rules apply with consideration of the specifics of bacterial and viral pathogens.

For suspected bacterial infections it is optimal to obtain diagnostic material from diseased animals before starting antibiotic treatment. In the case of section material, it is advisable to collect material in the transition area from changed to unchanged tissue. In the herd management, the diagnostic killing of animals with typical symptoms followed by immediate sample collection can be very advantageous. If test material is obtained from live animals, the most important factor is the method of collection. It must be oriented towards the expected pathogens, their sites of colonisation and the organs of manifestation. Microbiological findings from clinically healthy animals must be interpreted with particular caution.

After diagnosis of the pathogenic species, cultivated strains shall be differentiated according to the state of scientific knowledge, also taking into account the particularities of bacterial and viral infections. Special emphasis should be placed on the detection of pathogen-typical virulence factors or known serovars, etc. Each differentiation criterion is initially desirable, but each isolate must be critically evaluated based on all information from the laboratory (including necropsy) and the herd. The mere detection of genotypic differences does not automatically justify the assumption that antigenic and thus immunologically relevant differences are associated with them and that a strain must therefore be selected.

The decision on the selection of one or more strains as the basis for the production of an autogenous vaccine is made in consideration of the microbiological findings, the anamnestic report and all information on the clinical situation and available section reports. A decision must be made on the aetiological significance of the isolated pathogens for the present disease event. The sole diagnosis of pathogenic species in the examined sample is not sufficient. This is particularly true in the case of the detection of several pathogens and the consideration of the production of a

combination vaccine. The more specifically the isolates can be assigned as the cause of the disease in the respective herd, the greater the chances of success. There are no immunological findings from which an optimal or “permitted” number of different pathogen strains for an AV can be derived. The decisive factor is the probability that the selected strains are (co-)responsible for the herd-specific disease.

It is common practice for manufacturers to store selected bacterial strains in strain banks for a certain period of time and to use them to produce new batches for the same epidemiological unit. However, the strain spectrum in these stocks must be checked at regular intervals and updated if necessary. Anything else would contradict the idea of specificity or accuracy of fit of the AV for the current infection incidence in the herd. For similar reasons, antibiotic resistance is also checked regularly. There are certainly different opinions on the time periods, but 12 months should give a good orientation. One can also use the procedure for monitoring antibiotic resistance as a guide for these determinations. The seed-lot procedure is a proven basis for the production of licensed vaccines, but AVs do not require approval and therefore cannot be guided by all the regulations for approved vaccines.

Another important decision concerns the selection of adjuvants. Here, safety always takes precedence over efficacy, and precisely because there are no safety tests as in the approval procedure, the manufacturer must pay particular attention to the safety profile. It is not for nothing that aluminium-based adjuvants, which have played a central role in human and veterinary medicine for almost 100 years, dominate the AV because of their high safety. They particularly address the Th2-based immune response, which is the main focus of inactivated vaccines anyway (Gerdts 2015, Hogen Esch et al. 2018). Of course, this does not exclude other adjuvants for AVs, but their use requires good justification, which must take into account the pathogen(s) in question as well as the animal species and the age group or direction of use of the animals (e.g. fattening pigs or pregnant sows).

The production and use of AVs are the responsibility of the prescribing veterinarian, the diagnostician (microbiologist/virologist, pathologist) and the manufacturer, sometimes in collaboration, sometimes alone.

Cooperation between the prescribing veterinarian, diagnostician and manufacturer is crucial in selecting strains suitable for AV. This decision should then include the choice of adjuvant, if appropriate, unless the manufacturer uses a standard adjuvant.
The manufacturers are responsible for the production of the AV in compliance with the specific GMP rules.

The prescribing veterinarian is then responsible for the application of the AV, i.e. taking

into account the criteria of epidemiological unit, vaccination eligibility (ability to be vaccinated) of the animals, appropriate application and also the pre-testing of the safety on a small group of animals, with which at least acute adverse reactions can be detected within a few hours.

In the following sections, examples of the production of AVs from the point of view of manufacturers are listed according to animal species.

It must be decided in each individual case whether the veterinary indication and the legal prerequisites for the production of an autogenous vaccines are fulfilled.

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2.2 Examples for Autogenous Vaccines in different species

General remarks

The following AVs are listed as examples of applications from recent years. They do not claim to be exhaustive and are not to be understood as suggestions for application. No examination was made of the countries in which their application was permitted or would be permitted today on the basis of the respective legal situation.

Authors are specialists from EMAV-Member-Companies. This chapter is edited by the Practice Advisory Group of the EMAV.

Attention please:

In this chapter, examples of autogenous vaccines are given.
The applicability of these examples requires a current examination in each individual case by the prescribing veterinarian with regard to the primacy of the use of approved vaccines, if these are available.

2.2.1 Autogenous Vaccines for Poultry

2.2.1.1. Autogenous vaccines against Bordetella avium - infection in poultry

Disease/Indication
Bordetella avium-infection, Bordetellosis

Pathogen/Antigen(s)
Bordetella avium

Frequency/Importance
Frequent cause of disease in gallinaceous birds e.g. chickens and turkeys.

Clinical picture and Losses
Birds are depressed and show disease of the upper respiratory tract. Infected birds are susceptible to secondary infections.

Additional Information/Literature
Temple, L. M., et al. (1998). "*Bordetella avium* virulence measured in vivo and in vitro." Infection and immunity 66: 5244-5251.

Arp, L. H., and N. F. Cheville. (1984): Tracheal lesions in young turkeys infected with *Bordetella avium*. American journal of veterinary research 45: 2196-2200.

2.2.1.2 Autogenous vaccine against Ornithobacterium rhinotracheale - infection in poultry

Disease/Indication
Ornithobacterium rhinotracheale-infection

Pathogen/Antigen(s)
Ornithobacterium rhinotracheale.
So far 18 serotypes (A-R) have been described. There is only limited cross-protection between different serotypes.
Little is known about virulence factors.

Frequency/Importance
Frequent cause of disease in gallinaceous birds e.g. chickens and turkeys worldwide.

Clinical picture and Losses
Birds are depressed and can show inflammation of upper and lower respiratory tract ranging from sneezing to severe pneumonia. Severe arthritis can be observed in turkeys. Also, encephalomyelitis can occur. Secondary infections often complicate the disease and lead to increased mortality.

Additional Information/Literature
Van Empel, P. C. M., and H. M. Hafez (1999). *Ornithobacterium rhinotracheale*: a review. Avian pathology 28: 217-227.

2.2.1.3 Autogenous vaccines against Pasteurella multocida - infection in poultry

Disease/Indication
Pasteurella multocida-infection, fowl cholera, wattle disease

Pathogen/Antigen(s)
Pasteurella multocida
16 Heddleston types/ serotypes, 5 capsule types (A-F); 3 subspecies: *multocida, gallicida, septica*. The virulence is associated with the production of endotoxins, adhesins and other membrane proteins.

Frequency/Importance
One of the most important pathogens in poultry (layers, waterfowl, turkeys). High risk in free range husbandry. Virulent strains causing high mortality.

Clinical picture and Losses
Peracute infection with septicaemia and sudden high mortality. Chronic infections can be observed as well as local inflammations.

Additional Information/Literature
Glisson, John R (1998). Bacterial respiratory diseases of poultry. Poultry science 77: 1139-1142.

2.2.1.4 Autogenous vaccines against Riemerella anatipestifer - infection in poultry

Disease/Indication
Riemerella anatipestifer-infection, Riemerellosis

Pathogen/Antigen(s)
Riemerella anatipestifer
21 Serotypes known

Frequency/Importance
One of the most important pathogens in ducks. Geese and turkeys can be affected as well.

Clinical picture and Losses
Respiratory signs, lameness, central nervous signs. Mortality rate can be very high.

Additional Information/Literature
Pathanasophon, Pornpen, et al. (1969). Immunogenicity of *Riemerella anatipestifer* broth culture bacterin and cell-free culture filtrate in ducks.
Avian Pathology 25: 705-719.

Sandhu, Tirath S. (2008). *Riemerella anatipestifer* infection.
Diseases of poultry: 758-764.

Rubbenstroth, Dennis, et al. (2009). Pathogenesis *of Riemerella anatipestifer* in turkeys after experimental mono-infection via respiratory routes or dual infection together with the avian metapneumovirus.
Avian pathology 38.6: 497-507.

2.2.1.5 Autogenous vaccines against Erysipelothrix rhusiopathiae - infection in poultry

Disease/Indication
Erysipelothrix rhusiopathiae-infection

Pathogen/Antigen
Erysipelothrix rhusiopathiae

Frequency/Importance
Sporadically emerging pathogen, with high relevance in all types of poultry.

Clinical picture and Losses
Peracute courses with septicaemia and high mortality. Chronical courses with locomotive disorders/lameness can be observed as well.

Additional Information/Literature
Hafez, H.M. (2003). Emerging and re-emerging bacterial diseases in poultry: a review. Vet. Med. Austria / Wien. Tierärztl. Mschr. 90: 174-181.

Bobrek, K., A. Gaweł, and M. Mazurkiewicz (2013). Infections with *Erysipelothrix rhusiopathiae* in poultry flocks. World's Poultry Science Journal 69: 803-812.

2.2.1.6 Autogenous vaccines against Gallibacterium anatis - infection in poultry

Disease/Indication
Gallibacterium anatis-infection

Pathogen/Antigen(s)
Gallibacterium anatis
Two biovars: *G. anatis* biovar anatis, *G. anatis* biovar haemolytica

Frequency/Importance
Sporadic cause of disease in chickens, turkeys and waterfowl in Europe.

Clinical picture and Losses
Can cause depression, reduction of egg production, respiratory disease. Increased mortality particularly in association with other pathogens.

Additional Information/Literature
Neubauer, C., et al. (2009). Tissue distribution of haemolytic *Gallibacterium anatis* isolates in laying birds with reproductive disorders.
Avian Pathology 38: 1-7

2.2.1.7 Autogenous vaccine against Enterococcus spp. in poultry

Disease/indication
Septicaemia (1), Endocarditis (2), amyloid Arthropathy (3), Brain Necrosis, Encephalomalacia (4), liver granulomas (5)

Pathogen/Antigen/Serovar/Strain
Enterococcus spp.
Different species are published

Frequency and significance of disease
This ubiquitous bacterium causes often disorders in poultry when other triggers occur.

Clinical pictures, morbidity, mortality, losses
Acute form: septicaemia, depression, lethargy, lassitude, pale combs and wattles, ruffled feathers, diarrhoea, fine head tremors, sudden death in young chicks (7).
Subacute/ chronic form: depression, loss of body weight, lameness, head tremor, endocarditis, fever (6).

Additional Information/Literature
Abe, Y. K. Nakamura, M. Yamada, and Y. Yamamuto (2005). Encephalomalacia with *Enterococcus durans* infection in the brain stem and cerebral hemisphere in chick in Japan. Avian Dis 50: 139-141

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Landman, W. J. (1999). Amyloid arthropathy in chickens.
Vet Q 21 (3): 78-82.

2.2.1.8 Autogenous vaccine against E. coli in poultry

Disease/indication
Colisepticemia, coligranuloma, air sac disease (chronic respiratory disease, CRD), swollen- head syndrome, venereal colibacillosis, peritonitis, salpingitis, orchitis, osteomyelitis, synovitis, arthritis, omphalitis, panophthalmitis, enteritis and cellulitis of poultry (1, 2, 3, 4).

Pathogen/Antigen/Serovar/Strain
Escherichia coli, APEC -avian pathogenic *E. coli*
Different serovars and sequence types are published.

Frequency and significance of disease
One of the economically most important pathogens in poultry at any production level and at any age.

Clinical pictures, morbidity, mortality, losses
From inapparent to unresponsiveness, sudden death without any clinical signs, respiratory disorders, local fibrinous inflammation, lameness, enteritis, serofibrinous discharge from nostril and eyes, sneeze and cough, diarrhoea.
Morbidity and mortality differ depending on age, predisposing factors and degree of *E. coli* presents. Losses may arise up to 5% a day.

Additional Information/Literature
Arp, L. H. (1982). Effect of passive immunization on phagocytosis of blood- borne *E. coli* in spleen and liver of turkeys. Am J Vet Res 43: 1034- 1040

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Trampel, D. W. and R. W. Griffth (1997). Efficacy of aluminium hydroxide-adjuvanted *E. coli* bacterin in tufkeyin turkey poults. Avian Dis 41: 263- 268

Gyimah, J. E., B. Panigrahy, and J. D. Williams (1986). Immunogenicity of an *E. coli* multivalent pilus vaccine in chickens. Avian Dis 30: 687-689.

2.2.1.9 Autogenous vaccine against Salmonella in poultry

Disease/ Indication
Salmonella infections and Salmonellosis

Pathogen/Antigen/Serovar/Strain
More than 2500 different serovars of *Salmonella enterica* with the Subspecies *enterica, salame, houtenae, diarizonae, arizonae* and *indica* are published (1-4). Epidemiological characterization of strains with phage typing and other methods, increasing importance of Multilocus sequence typing (MLST).

Frequency and significance of disease
After introduction of an intensive vaccination and eradication program for. *S.* Pullorum, *S*. Gallinarum, *S*. Enteritidis and Typhimurium other serotypes as *S*. Hadar, Kentucky and Heidelberg (8) become more and more important. Beside the prevention of negative impacts for the birds, public health and legal requirements leads to an almost zero tolerance for any *Salmonella (5).*

Clinical pictures, morbidity, mortality, losses
Clinical signs depend on age, infectious dose and status of the individual microbiome (6). Gross lessons and microscopic lesions include peritonitis, perihepatitis, yolk sac infection, typhlitis, pneumonia, and enteritis. Mortality ranges from 8 to 60%. Latent infections are of public health concern.

Additional Information/Literature
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Malorny B., Hauser E., Dieckmann R. (2011). New approaches in subspecies-level *Salmonella* classification. In: Porwollik S., editor. Salmonella from Genome to Function. Norfolk, UK: Academic Press; 2011. pp. 1-23.

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Parimal Roy, Tamil Nadu, A S Dhillon, H L Shivaprasad, D M Schaberg (2001). Pathogenicity of Different Serogroups of Avian Salmonellae in Specific-Pathogen-Free Chickens, October 2001, Avian Diseases 45(4):922-37. DOI 10.2307/1592871

S. D. Young, O. Olusanya, K. H. Jones, T. Liu, K. A. Liljebjelke, C. L. Hofacre (2007). *Salmonella*-Incidence in Broilers from Breeders Vaccinated with Live and Killed-*Salmonella.* Journal of Applied Poultry Research, Volume 16, Issue 4, 1 December 2007, Pages 521-528

2.2.1.10 Autogenous vaccine against Adenovirus in chicken

Disease/indication
Inclusion body hepatitis, Hepatomegaly, Gizzard erosion, Hydropericard, Diarrhoea, Icterus, Pancreatitis, Tenosynovitis in chicken, turkeys, ducks, geese, quails, ostriches and pigeons (1-3)

Pathogen/Antigen/Serovar/Strain
Adenovirus subgroup FAdV-1 with 12 different serovars or 5 genotypes A-E (4)

Frequency and significance of disease
Widely spread in poultry, important pathogen especially when immunosuppressive factors trigger the disease.

Clinical pictures, morbidity, mortality, losses
100% Morbidity, Sudden onset of mortality up to 10%, ruffled feathers, lethargy, diarrhoea, retarded growth, tenosynovitis, respiratory signs, vomiting

Additional Information/Literature
Benko, M., B. Harrach, and W. C. Russel (2001). Family A*denoviridae*. In M. H. V. Van Regenmortel, C. M. Fauquet, D. H. L. Bishop, E. B. Carstens, M. K. Estes, S. M. Lemon, J. Maniloff, M. A. Mayo, D. J. McGeoch, C. R. Pringle, R. B. Wickner (eds.): Virus Taxonomy. Seventh Report of international Committee on Taxonomy of Viruses. Academic Press: New York and San Diego. 227-238.

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McFerran, J. B. (1981). Adenoviruses of vertebrate animals. In E. Kurstak and C. Kurstak (eds.). Comparative Diagnosis of Viral Diseases III. Academic Press: New York, 102-165.

2.2.1.11 Autogenous vaccines against Infectious Bronchitis Virus - infection in chicken and turkeys

Disease/Indication
Avian infectious bronchitis virus

Pathogen/Antigen(s)
Chicken aCoV / IBV
Turkey TCoV

Variants (Europe)
- D274 – D207
- D1466
- 4/91 (793B)
- QX (D388)
- Massachusetts
- Italy02
- D181
- IB80

Frequency/Importance
Enormous capacity to change by spontaneous mutation and genetic recombination – relevant for emergence of new variants
Low mortality but high morbidity and significant economic impact
- Boilers: poor weight gains, condemnation, mortality
- Layers: suboptimal egg production, downgrading of eggs

Clinical picture and Losses
Respiratory disease – mortality between 5-25% in chronic cases, important concurrent infections (*E. coli*)
- Difficulty breathing
- Tracheal rales
- Coughing
- Sneezing
- General weakness
- Depression
- Congested trachea (tracheal lesions)

Reproductive disorder
- Drop in egg production by 3-10%, up to 50% observed in most severe cases.
- Varies depending on stage of lay and variant
- Smaller eggs, lower quality: soft-pale-shelled and misshapen

Nephritic disease
- Mild and transient respiratory signs
- Enlarged kidneys
- Ruffled feathers
- Rapid weight loss
- Diarrhoea (wet litter)
- Dry and dark carcasses

Additional Information/Literature

Guys JS (2000). Turkey coronavirus is more closely related to avian infectious bronchitis virus than to mammalian coronaviruses: a review. Avian Pathol. 29(3):207-12. DOI 10.1080/03079450050045459

Sjaak de Wit JJ et. al. (2011). Infectious bronchitis virus variants: a review of the history, current situation and control measures. Avian Pathol. 40(3):223-35. DOI 10.1080/03079457.2011.566260

J. Ignjatovic, S. Sapats (2000). Avian infectious bronchitis virus. Rev. sci. tech. Off. Int. Epiz. 19(2), 493-508

2.2.1.12 Autogenous vaccines against Duck Hepatitis Virus - infection in ducks

Disease/Indication
Duck viral hepatitis

Pathogen/Antigen(s)
Duck hepatitis A virus (DHAV)
3 genotypes
- DHAV-1 – most widespread and virulent
- DHAV-2 and -3

Frequency/Importance
Acute, typically affecting ducklings up to 6w of age
Highly contagious
High mortality (up to 100%)

Clinical picture and Losses
Ducklings
- Lethargic
- Lose balance
- Enlarged liver covered with haemorrhagic foci
- Kidneys and spleen might be enlarged

Clinical signs not seen in ducks over 7w of age

Additional Information/Literature
Yugo M.D. et. al. (2016). Hepatitis Virus Infections in Poultry.
Avian Dis. 60(3):576-88.

Niu Y. et. al. (2019). The pathogenicity of duck hepatitis A virus types 1 and 3 on ducklings. Poultry Science, Volume 98, Issue 12, 6333-6339.

2.2.1.13 Autogenous vaccines against Reovirus - infection in chicken and turkeys

Disease/Indication
Avian Orthoreovirus infection

Pathogen/Antigen(s)
Avian reovirus (ARV)
Several genotypes known, distributed in 6 clusters.

Frequency/Importance
Ubiquitous in poultry flocks
Low morbidity and mortality
Extreme variability – emergence of ARV variants
Involved in severe disease syndromes such as viral arthritis (tenosynovitis) and malabsorption syndrome
Economic losses - production can be affected (poor growth and feed conversion, increased condemnations)

Clinical picture and Losses
Viral arthritis / Tenosynovitis – predominant in broilers
- Leg weakness
- Swelling of hock joints
- Acute lameness
- Immobilization

Malabsorption syndrome (MAS)

Additional Information/Literature
Jones, R. C. (2000). Avian reovirus infections. Rev. sci. tech. Off. int. Epiz.19 (2), 614-625

Egaña-Labrin, S. et. al. (2019). Genotypic Characterization of Emerging Avian Reovirus Genetic Variants in California. Scientific Reports 9:9351

2.2.1.14 Autogenous vaccines against Low Pathogenic Influenza - infection in chicken and turkeys

Disease/Indication
Low pathogenic Avian Influenza (LPAI)

Pathogen/Antigen(s)
Low Pathogenic Influenza A- Avian influenza (LPAI)
Multiple subtypes depending on HA (18 subtypes) and NA (11 subtypes) combinations. Practical importance and need especially in case of LPAI-types H1, H3, H6 and H9. Not applicable in case of HPAI = certain H5/H7

Frequency/Importance
LPAI-infections with H-types H1, H3, H6 (in turkeys) or H9 (in chickens and turkeys) are able to induce a drop in egg production as well as a mortality.
Infection of birds with LPAI of types H5 and H7 may result in virus mutation, creating an HPAI. Any production of autogenous vaccines based on LPAI-isolates of types H5 or H7 is out of question and is to be rejected.
Zoonotic: important consequences possible (Example: H5N1 and H7N9 outbreaks in humans). Control and surveillance are of outmost importance.

Note the current legal situation about vaccination! Vaccinations can only be allowed or even prohibited under certain conditions.

Clinical picture and Losses
LPAI: Ruffled feathers
Drop in egg production
Nasal discharge
Coughing
Sneezing
Mortality

Additional Information/Literature
Thomas J.K, et al. (2007). Avian influenza: a review. Am J Health Syst Pharm. 15;64(2):149-65. DOI 10.2146/ajhp060181

Nuñez I.A. et. Al. (2019). A review of H5Nx avian influenza viruses.
Ther Adv Vaccines Immunother. 7

EU (2022). Council approves conclusion on a strategic approach for the development of vaccination as a complementary tool for the prevention and control of highly pathogenic avian influenza (HPAI). Press office – General Secretariat of the Council. 24.5.2022. www.consilium.europa.eu

2.2.1.15 Autogenous vaccines against Goose Haemorrhagic Polyomavirus

Disease/Indication
Haemorrhagic Nephritis Enteritis of Geese (HNEG)

Pathogen/Antigen(s)
Goose Haemorrhagic Polyomavirus

Frequency/Importance
High morbidity and mortality rates in geese 4 to 10 weeks old. Under field conditions, death is the most common outcome, generally preceded by ataxia or coma.

Clinical picture and Losses
Acute:
- Sudden death
- Ataxia
- Reddish mucosa of the intestines
- Reddish discolouration of the swollen kidneys
- Oedema and haemorrhages of the subcutaneous connective tissue
- Hydropericardium
- Ascites

Subacute cases:
- Visceral gout

Additional Information/Literature
Palya V., Ivanics É., Glávits R., Dán Á., Mató T., Zarka P. (2004). Epizootic occurrence of haemorrhagic nephritis enteritis virus infection of geese. Avian Pathology, 33:2, 244-250, DOI 10.1080/0307945042000195740

2.2.2 Autogenous Vaccines for Pigs

2.2.2.1 Autogenous vaccines against infections with *Brachyspira spp.* in pigs

Disease/Indication
Swine dysentery (SD), porcine intestinal spirochaetosis

Pathogen/Antigen(s)
Brachyspira (B.) hyodysenteriae (classical SD), *B. pilosicoli* (porcine intestinal spirochaetosis), *B. suanatina* (SD like), *B. hampsonii* (SD like), *B. murdochii* (occasionally mild colitis), *B. intermedia* (significance in pigs unclear), *B. innocens* (commensal).

Brachyspira is a genus of bacteria classified within the phylum Spirochaetes. *Brachyspira spp.* are gram-negative, oxygen-tolerant, anaerobic spirochetes. Brachyspira are large, loosely coiled spirochaetes ranging in size from 2 to 13 µm in length and from 0.2 to 0.4 µm in width. *B. hyodysenteriae* is β-haemolytic on sheep blood agar and haemolysins are believed to be important virulence factors.

Frequency/Importance
SD as well as porcine intestinal spirochaetosis have a worldwide distribution and are endemic in many countries where they can cause substantial financial losses through reduced and uneven growth rates, mortalities, costs of treatment and impediment to trade. The diseases also may become a welfare issue where it is not effectively controlled. The reported prevalence of *B. hyodysenteriae* ranges from 0% to near 40%. Variations in prevalence can be due to the use of different diagnostic methods, or to differences among countries in housing, management, feeding regimes, etc. Moreover, whereas in many countries the prevalence may be concealed by the use of antimicrobials as feed additives, in others the ban of antibiotics as growth promoters may have resulted in an increase in SD prevalence. *B. hyodysenteriae* has been traditionally considered a pathogen mainly transmitted by direct contact, through the introduction of subclinically infected animals into a previously uninfected herd. However, recent findings position *B. hyodysenteriae* as a potential threat for indirect transmission between farms, i.e., it can survive for long periods of time in pig faeces, and it has been found in feral pigs, laying chickens, mallards, rheas, seagulls, rodents, dogs, flies and other insects.

Clinical picture and Losses
Classical SD is a severe enteric disease in pigs, which is characterized by bloody to mucoid diarrhoea and associated with reduced growth performance and variable

mortality. This disease is most often observed in grower–finisher pigs, wherein susceptible pigs develop a significant muco-haemorrhagic typhlocolitis following infection with strongly haemolytic *B. hyodysenteriae* strains. On the other hand, the disease may be mild and/or not clinically apparent in some herds. In the early 2000s two newly described strongly haemolytic pathogenic *Brachyspira spp*., *Brachyspira suanatina* and *Brachyspira hampsonii*, were associated to cause a disease indistinguishable from SD. Both of which appear to have reservoirs in migratory waterbirds and may be transmitted to and between pigs. *B. suanatina* seems to be confined to Scandinavia, whereas *B. hampsonii* has been reported in North America and Europe. *B. pilosicoli* was clearly confirmed as being an enteric pathogen in pigs, causing a mild colitis and a diarrhoeal disease called porcine intestinal spirochaetosis. *B. murdochii*, although generally considered a commensal, occasionally has been associated with mild colitis in swine. The significance of *B. intermedia* in pigs is unclear. *B. innocens*, a weakly haemolytic spirochaete, had been isolated from healthy pigs and is considered to not cause disease.

Additional Information/Literature

Hampson et al. Emergence of Brachyspira species and strains: reinforcing the need for surveillance. Porcine Health Management (2015), 1:8

E. R. Burrough. Swine Dysentery: Etiopathogenesis and Diagnosis of a Reemerging Disease. Veterinary Pathology (2017), 54(1): 22-31

Alvarez-Ordóñez et al. Swine Dysentery: Aetiology, Pathogenicity, Determinants of Transmission and the Fight against the Disease. Int. J. Environ. Res. Public Health (2013), 10: 1927-1947

2.2.2.2 Autogenous vaccines against teschovirus encephalomyelitis/Talfan disease caused by porcine teschovirus type 1

Disease/Indication
Teschovirus encephalomyelitis, Talfan disease (benign enzootic paresis)

Pathogen/Antigen(s)
Porcine Teschovirus type 1 (PTV-1), non-enveloped RNA virus, genus *Teschovirus*, family *Picornaviridae*

Frequency/Importance
Highly virulent strains of PTV-1 are known for causing teschovirus encephalomyelitis. Less virulent strains of PTV-1, in addition to PTV-2, PTV-3, and PTV-5, are associated with Talfan disease (also known as benign enzootic paresis), a milder presentation of polioencephalomyelitis than teschovirus encephalomyelitis. PTV is endemic in most conventional swine herds throughout the world. Teschovirus encephalomyelitis causes high morbidity and mortality in all age groups. Recent outbreaks of the disease were reported in Haiti, Canada, Spain, Brazil and the Netherlands. Talfan disease is associated with low morbidity and mortality and clinical disease is generally limited to younger, post-weaning animals.

Clinical picture and Losses
Faecal-oral transmission of PTV is most common. However, PTV is persistent in the environment and fomites likely play a role in transmission as well. PTV infections are often asymptomatic, but in addition to polioencephalomyelitis, they can also induce a broad range of clinical syndromes including reproductive disorders, pneumonia, enteric disease, and pericarditis. In teschovirus encephalomyelitis, fever, inappetence, lethargy, and ataxia may be seen prior to paralysis or paresis. Paralysis begins in the hind limbs and travels cranially; once the respiratory muscles are involved the animal dies of suffocation. Reproductive disorders associated with PTV infection have been termed “SMEDI syndrome” (stillbirth [S], mummified foetus [M], embryonic death [ED], infertility [I]). There are no clinical signs seen in gilts or sows with SMEDI syndrome. When pericarditis or myocarditis is present, it is generally accompanied by polioencephalomyelitis.

Additional Information/Literature
Horak S, Killoran K, Leedom Larson KR. Porcine teschovirus. Swine Health Information Center and Center for Food Security and Public Health, 2016. http://www.cfsph.iastate.edu/pdf/shic-factsheet-porcine-teschovirus

Alexandersen S, Knowles NJ, Dekker A, Belsham GJ, Zhang Z, Koenen F.

Picornaviruses. In: Zimmerman JJ, Karriker LA, Ramirez A, Schwartz KJ, Stevenson GW, eds. Diseases of Swine. 11 ed: John Wiley & Sons, Inc.; 2019

Deng MY, Millien M, Jacques-Simon R, Flanagan JK, Bracht AJ, Carrillo C, Barrette RW, Fabian A, Mohamed F, Moran K, Rowland J, Swenson SL, Jenkins-Moore M, Koster L, Thomsen BV, Mayr G, Pyburn D, Morales P, Shaw J, Burrage T, White W, McIntosh MT, Metwally S. Diagnosis of Porcine teschovirus encephalomyelitis in the Republic of Haiti. J Vet Diagn Invest. 2012;24(4):671-678

Salles MWS, Scholes SFE, Dauber M, Strebelow G, Wojnarowicz C, Hassard L, Acton AC, Bollinger TK. Porcine teschovirus polioencephalomyelitis in western Canada. J Vet Diagn Invest. 2011;23(2):367-373

Vreman et al. Two novel porcine teschovirus strains as the causative agents of encephalomyelitis in the Netherlands. BMC Veterinary Research 2020; 16:51

2.2.2.3 Autogenous vaccines against suckling piglet diarrhoea caused by group A Rotavirus (RVA)

Disease/Indication
Acute viral gastroenteritis, suckling piglet diarrhoea

Pathogen/Antigen(s)
Group A rotavirus (RVA), family *Reoviridae*, genus *Rotavirus* (dsRNA virus)

Frequency/Importance
Group A rotavirus (RVA) infections cause severe economic losses in intensively reared livestock animals, particularly in herds of swine and cattle. RVA strains are antigenically heterogeneous, and are classified in multiple G and P types defined by the two outer capsid proteins, VP7 and VP4, respectively. RVA is a major cause of acute neonatal diarrhoea in piglets and it is present in most if not all pig herds.

Clinical picture and Losses
The virus is transmitted by the faecal-oral route and the infection results in destruction of mature small intestinal enterocytes. Loss of villous epithelium results in partial villous atrophy, malabsorption, and osmotic diarrhoea. If neonatal pigs do not receive protective levels of maternal antibodies, they are likely to develop profuse watery diarrhoea within 12-48 hours after infection. Diarrhoea usually persists for 2-5 days. Diarrheic piglets become dehydrated, gaunt and rough-haired, but mortality usually is low. However, secondary infections with bacterial pathogens such as enterotoxigenic *E. coli* or *Clostridia spp.* are frequent and might aggravate the clinical outcome.

Additional Information/Literature
Papp H, László B, Jakab F, et al. Review of group A rotavirus strains reported in swine and cattle. Vet Microbiol. 2013;165(3-4):190-199
DOI 10.1016/j.vetmic.2013.03.020

Vlasova AN, Amimo JO, Saif LJ. Porcine Rotaviruses: Epidemiology, Immune Responses and Control Strategies. Viruses. 2017;9(3):48 DOI 10.3390/v9030048

2.2.2.4 Autogenous vaccines against Glaesserella parasuis - infection

Disease/Indication
Glässer´s disease

Pathogen/Antigen(s)
Glaesserella parasuis formerly known as *Haemophilus parasuis*;
15 known serovars

Frequency/Importance
Significant disease in modern age-segregated production systems worldwide.

Clinical picture and Losses
Mortality and morbidity vary from 5-10 % to 75 %;
Mainly observed in 4 to 8-week-old pigs:

Peracute	Acute	Chronic
Sudden death	high fever, coughing, abdominal breathing, swollen joints with lameness, central nervous signs	rough hair, reduced growth rate, lameness

Additional Information/Literature
Aragon V, Segales J, Oliveira S. Glaesser's Disease. In: Diseases of Swine, 10th Edition edn. J. Zimmerman LK, A. Ramirez, K. Schwartz, G. Stevenson, 11ed. Iowa, USA: John Wiley & Sons, Inc 2019: 760-9

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2.2.2.5 Autogenous vaccines against porcine Influenza virus A - H1pdmN2 infection (and other Swine Influenza viruses)

Disease/Indication
Swine Influenza; *Swine Influenza virus (SIV) A - H1pdmN2*

Pathogen/Antigen(s)
Swine Influenza type A subtype H1pandemicN2 virus, genus *Orthomyxovirus*, family *Orthomyxoviridae*.
Polymorphic, enveloped, segmented RNA-virus; high degree of genetic reassortment.

In 2009, an H1N1 subtype of the pig was declared pandemic by the World Health Organization. Pig influenza viruses can be transmitted to humans and are therefore potentially zoonotic. The pig is also described as a "reassortant vessel" in which human, poultry and pig influenza viruses can recombine and form into a potentially new subtype. In 2012, a new reassortment between H1N1pdm and HxN2 was performed with the result of the new subtype H1pdmN2. The HA protein of the H1pdmN2 reassortants has undergone significant changes and can also be distinguished antigenically from the original H1pdmN2 of human origin.

The following subtypes have been described for pigs so far: H1N1, H1N2, H3N2, H1pdmN1pdm, H1pdmN2

Frequency/Importance
Frequent pathogen in pigs of all ages worldwide; H1pdmN2 is widespread regionally, especially in north-western Germany.
Circulation in the stockpiles lead to new outbreaks at regular intervals.

Clinical picture and Losses
High fever, anorexia, inactivity, huddling, reluctance to rise, tachypnoea, coughing; high morbidity, low mortality; part of the Porcine Respiratory Disease Complex (PRDC); in piglet rearing flocks the high fever can lead to abortions, stillbirths and births of weak piglets.

Additional Information/Literature
Rewar, S., Mirdha, D., Rewar, P. (2015): Treatment and Prevention of Pandemic H1N1 Influenza. Annals of Global Health, 81: 645-653

Baudon, E., Peyre, M., Peiris, M., Cowling B.J. (2017): Epidemiological features of influenza circulation in swine populations: A systemic review and meta-analysis.
Plos One, 12: e0179044 (1-25)

Janke, B.H. (2014): Influenza A Virus Infections in Swine: Pathogenesis and Diagnosis. Veterinary Pathology, 51: 410-426

Sinha, M. (2009): Swine flu. Journal of Infection and Public Health, 2: 157-166.
Thacker E, Janke B. 2008. Swine influenza virus: zoonotic potential and vaccination strategies for the control of avian and swine influenzas. J. Infect. Dis. 197(Suppl 1): 19-24

Starick E, Lange E, Grund C, Grosse Beilage E, Döhring S, Maas A, et al. Reassortants of pandemic influenza A virus H1N1/2009 and endemic porcine HxN2 viruses emerge in swine populations in Germany. J Gen Virol. 2012; 93: 1658-63. PMID: 22622326

Lange J, Groth M, Schlegel M, Krumbholz A, Wieczorek K, Ulrich R, et al. Reassortants of the pandemic (H1N1) 2009 virus and establishment of a novel porcine H1N2 influenza virus, lineage in Germany. Vet Microbiol. 2013; 167: 345-56. PMID: 24139631

Harder TC, Grosse Beilage E, Lange E, Meiners C, Döhring S, Pesch S, et al. Expanded cocirculation of stable subtypes, emerging lineages, and new sporadic reassortants of porcine influenza viruses in swine populations in Northwest Germany. J Virol. 2013; 87: 10460-76. PMID: 23824819

2.2.2.6 Autogenous vaccines against Streptococcus-suis - infections in pigs

Disease/Indication
Streptococcus-suis-infection

Pathogen/Antigen(s)
Streptococcus suis
29 to 35 Serotypes, worldwide serotype 2 most frequently isolated from clinical cases, in Europe also serotypes 7 and 9 are important.
Virulence associated antigens: MRP (muramidase-released protein), EF (extracellular factor), Suilysin (haemolysin), IgM-Protease Ide_{Ssuis}

Frequency/Importance
One of the most important pig pathogens.

Clinical picture and Losses
Meningitis, arthritis and septicaemia in piglets, mainly at the age of 4 to 10 weeks.

Additional Information/Literature
Unterweger, C.; Baums, C.; Höcher, M.; Fischer, L.; Weiss, A.; Hennig-Pauka, I. (2014): Clinics, diagnosis and prophylaxis of a *Streptococcus suis* serotype 7 farm problem. Berl. Münch. Tierärztl. Wschr. 127: 194-201
DOI 10.2376/0005-9366-127-194

Rieckmann, K.; Pendzialek, S.-M.; Vahlenkamp, T.; Baum, C. G. (2020): A ciritcal review speculating on the protective efficacies of autogenous *Streptococcus suis* bacterins as used in Europe. Porcine Health Managment 6:12
DOI 10.1186/s40813-020-00150-6

Rieckmann, K. L. M. (2020): Characterization of neglected Streptococcus suis pathotypes: molecular epidemiology and IdeSsuis-based vaccination approaches. Inaugural Dissertation, Universität Leipzig

2.2.2.7 Autogenous vaccines against Streptococcus dysgalactiae subsp. equisimilis - infection

Disease/Indication
Streptococcus dysgalactiae subsp. *equisimilis* - infection

Pathogen/Antigen(s)
Streptococcus dysgalactiae subsp. *equisimilis*
Gram-positive, coccoid bacteria; beta-haemolytic streptococci belonging to Lancefield group C, G or L

Frequency/Importance
Member of the normal flora; considered the most important beta-haemolytic streptococci in pigs.

Clinical picture and Losses
Infection is usually seen in pigs between 1 and 3 weeks of age. Joint swelling and lameness are the most obvious and persistent clinical signs; infrequently *Streptococcus suis* - like clinical signs.

Additional Information/Literature
Hommez J, Devriese L, Castryck F, Miry C (1991) Bèta-hemolytic streptococci from pigs: bacteriological diagnosis. J Vet Med B 38:441-444

C. Helmer et al (2019): Analysis of 719 *Streptococcus* species strains gained from diseased pigs showing *Streptococcus suis* - like symptoms in 2017. Accepted Poster ESPHM Utrecht 2019

Woods R, Ross RF. (1977): Immunogenicity of experimental *Streptococcus equsimilis* vaccines in swine. AM J Vet Res 38:33-36.

2.2.2.8 Autogenous vaccines against Mycoplasma-hyosynoviae- and Mycoplasma-hyorhinis - infections in pigs

Disease/Indication
Mycoplasma-Polyarthritis – *Mycoplasma hyorhinis*
Mycoplasma-Polyserositis – *Mycoplasma hyosynoviae*

Pathogen/Antigen(s)
M. hyorhinis, M. hyosynoviae
In sows both species can be isolated from the same animal.

Frequency/Importance
Frequent pathogens in younger pigs.

Clinical picture and Losses
M. hyorhinis -Polyarthritis and polyserositis in pigs mainly between (3)-6 und 10 weeks. Association with pneumonic processes is possible.
M. hyosynoviae – Non-purulent polyarthritis in pigs between 3 and 6 months and gilts.

Additional information/Literature
Roos, L. R.; Nair, M. S.; Rendahl, A. K.; Pieters, M. (2019): *Mycoplasma hyorhinis* and *Mycoplasma hyosynoviae* dual detection patterns in dams and piglets. PLOS ONE 03.01.2019. DOI 10.1371/journal.pone.0209975.

2.2.2.9 Autogenous vaccines against Staphylococcus-hyicus - infections in pigs

Disease/Indication
Greasy Pig Disease, Exudative Epidermitis, Marmite Disease, *Staphylococcus-hyicus*-infection

Pathogen/Antigen(s)
Staphylococcus hyicus
Strains of different virulence, virulent strains produce Exfoliative Toxins.

Frequency/Importance
Important skin pathogen in young pigs. Sporadic endemic herd problem.

Clinical picture and Losses
Generalized or localized skin disease of suckling and weaned pigs up to 6 weeks, seldom in older pigs. Most severe cases and deaths in younger animals.

Additional Information/Literature
Arsenakis, I.; Boyen, F.; Haesebrouk, F.; Maes, D. G. D. (2018): Autogenous vaccination reduces antimicrobial usage and mortality rates in a herd facing severe exudative epidermitis outbreaks in weaned pigs. Vet. Rec. 182 (26): 744.
DOI 10.1136/vr.104720.

2.2.2.10 Autogenous vaccines against *Actinobacillus suis* - infections in pigs

Disease/Indication
Cystitis and pyelonephritis in sows, caused by *Actinobacillus suis*
Septicaemia in piglets, caused by *Actinobacillus suis*

Pathogen/Antigen(s)
Actinobacillus (A.) suis
Formerly known as: *Eubacterium suis, Actinomyces suis, Corynebacterium suis*

Frequency/Importance
Pigs are the main host for *A. suis* and the majority of boars over 6 months of age carry them in their preputial diverticulum.

Clinical picture and Losses
Infections with *A. suis* in sows lead to ascending urinary tract infections (Cystitis and pyelonephritis). Affected sows show signs of depression, haematuria, vaginal discharge, and weight loss. Sows die frequently due to renal failure.

Infections with *A. suis* in piglets can lead to foetal septicaemia with signs of cyanosis, respiratory distress central nervous disturbances or sudden death. Less affected piglets show mild cough, fever, and anorexia.

Additional Information/Literature
Van Ostaaijen et al. (1997). Actinobacillus suis strains isolated from healthy and diseased swine are clonal and carry apxICABDvar. suis and apxIICAvar. suis toxin genes. Journal of clinical microbiology, 35:5

Ojha et al. (2010). Characterization of colonization-deficient mutants of *Actinobacillus suis.* Veterinary microbiology, 140; 1-2

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2.2.2.11 Autogenous vaccines against Actinomyces hyovaginalis - infections in pigs

Disease/Indication
Pyemic lesions and reproductive failure in pigs caused by *Actinomyces hyovaginalis*

Pathogen/Antigen(s)
Actinomyces hyovaginalis

Frequency/Importance
Actinomyces hyovaginalis is very widespread among pigs and can be differentiated into a “general” biotype and a “vaginal” biotype. Both are reported to be commensal colonizers of various pig tissue but also to be the cause of severe clinical disease.

Clinical picture and Losses
The clinical signs of infections with *Actinomyces hyovaginalis* mainly include abortions in sows and pyemic lesions in different organs of pigs, with lung lesions being the most reported (disseminated necrotic lesions and abscesses).

Additional Information/Literature
Aalbæk et al. (2003). *Actinomyces hyovaginalis* - Associated with Disseminated Necrotic Lung Lesions in Slaughter Pigs. Journal of comparative Pathology, 129:1

Broes et al. (2019). Miscellaneous bacterial infections. In: Zimmermann et al. (2019): Diseases of Swine.

Storms et al. (2002). Identification of a new biotype of *Actinomyces hyovaginalis* in tissues of pigs during diagnostic bacteriological examination. Vet Microbiol 84: 93-102. DOI 10.1016/s0378-1135 (01) 00438-2

2.2.2.12 Autogenous vaccines against Encephalomyocarditis virus - infections in pigs

Disease/Indication
Infections with the Encephalomyocarditis Virus in swine

Pathogen/Antigen(s)
Encephalomyocarditis Virus *(Picornaviridae)*

Frequency/Importance
The Encephalomyocarditis Virus is associated with increased incidence of sudden death as well as reproductive losses in swine worldwide. Increased mortality rates can lead to significant economic losses in affected herds. Although the virus was originally thought to spread in tropical and subtropical regions, the pathogen is now spreading in various regions of the world including Europe.

Clinical picture and Losses
Hydropericardium, hydrothorax, and pulmonary oedema along with multifocal necrotic foci in the myocardium are the most common pathologic findings in Encephalomyocarditis Virus infection of young pigs. Transplacental transmission to the foetus may result in abortion of haemorrhagic, oedematous, mummified, or even apparently unchanged piglets.

Additional Information/Literature
Alexandersen et al. (2019). Picornaviruses. In: Zimmermann et al. (2019): Diseases of Swine.

Jeoung et al. (2012). A novel vaccine combined with an alum adjuvant for porcine encephalomyocarditis virus (EMCV)-induced reproductive failure in pregnant sows. Research in Veterinary Science, 93:3

2.2.2.13 Autogenous vaccines against Enterococcus hirae, Enterococcus villorum and Enterococcus durans - infections in pigs

Disease/Indication
Neonatal Porcine Diarrhoea Syndrome

Pathogen/Antigen(s)
Enterococcus durans
Enterococcus hirae
Enterococcus villorum

Frequency/Importance
Suckling piglet diarrhoea in the first weeks of life is a widespread disease in swine herds and can lead to significant economic losses. Furthermore, it is an impairment of animal welfare by increased mortality and decreased weight gain. *Enterococcus durans*, *Enterococcus hirae*, *Enterococcus villorum* – among other pathogens – are known to be responsible for neonatal diarrhoea in suckling piglets.

Clinical picture and Losses
The presence of Enterococci increases the risk of suffering from suckling piglet diarrhoea. Enterococci are colonizing the small intestine and thereby cause mucosal lesions, leading to diarrhoea. *E. hirae* and *E. durans* can cause villous atrophy. Furthermore, it is discussed that *E. durans* acts as a primary pathogen with the ability to pave the way for other pathogens (e.g., *E. coli*).

Additional Information/Literature
D-S. Cheon, C. Chae (1996). Outbreak of diarrhea associated with Enterococcus durans ins piglets. J Vet Diagn Invest 8:123-124

M. Gottschalk, M. Seguara (2019). Streptococcosis. In: Zimmermann et al. (2019): Diseases of Swine

M-L. Hermann-Blank et al. (2015). Characterization of the bacterial gut microbiota of piglets suffering from new neonatal porcine diarrhoea. BMC Vet. Res 11:139

B. Jonach et al. (2014). Fluorescence in situ hybridization investigation of potentially pathogenic bacteria involved in neonatal porcine diarrhea. BMC Vet. Res. 20:68

J. Larsson et al. (2014). Neonatal Piglet Diarrhoea Associated with Enteroadherent Enterococcus hirae. J Comp Path. 1151:137-47

2.2.2.14 Autogenous vaccines against Trueperella abortisuis in pigs

Disease/Indication
Reproductive symptoms: abortion
Cystitis in sows

Pathogen/Antigen(s)
Trueperella abortisuis
Formerly known as: *Arcanobacterium abortisuis*

Frequency/Importance
Several cases of abortions causally related to *Trueperella abortisuis* have been described.

Clinical picture and Losses
Trueperella abortisuis causes abortion in pigs. Pathological alterations were described with thickened, white placentas. Histologically placentitis is described, as well as subcutaneous oedema and increased fluids in the body cavities of aborted foetuses. *Trueperella abortisuis* has been found in the placenta and vaginal discharge of sows as well as in the tissue of aborted litters. Furthermore, it could be isolated from boar sperm.

Additional Information/Literature
M. Alssahen et al. (2019). Epidemiological analysis of *Trueperella abortisuis* isolated from cases of pig abortion of a single farm. Folia Microbiol (Praha) 65(3):491-496

R. Azuma et al. (2009). *Arcanobacterium abortisuis* sp. nov., isolated from placenta of a sow following an abortion. Int J Syst Evol Micrbiol. 59(6):1469-73

A. Broes et al. Miscellaneous Bacterial Infections. In: Zimmermann et al. (2019): Diseases of Swine. 11ed, John Wiley &Sons

Unpublished Authors: *Trueperella abortisuis* causing abortion in pigs in Scotland. (2019). Vet Record Volume 185, 6:162-165

2.2.3 Autogenous Vaccines for Cattle

2.2.3.1 Autogenous vaccines against Mycoplasma bovis - infection in cattle

Disease/Indication
Bovine Mycoplasmosis - Pneumonia
Otitis media and internal (with possible meningitis)
Mastitis
(Poly)Arthritis
Reproductive disease
Infectious Keratoconjunctivitis

Pathogen/Antigen(s)
Mycoplasma bovis

Frequency/Importance
This bacterium is considered to be one of the major emerging pathogens of cattle in industrialized countries threatening livestock production. It is increasingly recognized by the veterinary and livestock communities as having an important impact on the health, welfare, and productivity of dairy and beef cattle.

Disease becomes usually chronical leading to subclinical carriers. *M. bovis* resides intracellularly in peripheral blood cells resulting to an “immune evasion”. Therefore, the laboratory diagnosis of the infection or the carriage can be difficult.

Clinical picture and Losses

Mastitis	Pneumonia	Arthritis	Otitis
Highly contagious *Multiple quarters affected* *Fever and pain* *Altered milk consistency (watery to purulent)* *Severe drop in milk production* *Subclinical (carrier) often have an increase of somatic cell count, a drop of production and lower fat/urea content in milk* *M. bovis mastitis is considered as untreatable leading to cull the infected animals*	*Young calf between 2 to 6 weeks* *Fever, anorexia, dyspnoea, depression, coughing and rhinorrhoea.* *The reduction of the immunological reaction facilitates the infection by other pathogens.* *Possible lesions: suppurative bronchopneumonia without necrosis, caseonecrotic bronchopneumonia, bronchopneumonia with coagulation necrosis foci and chronic bronchopneumonia with subsequent abscessation.*	*Mainly Calves* *Usually located to shoulder, elbow, and /or knee* *Fever and pain* *Pyogranulomatous to serofibrinous synovitis*	*Calves* *Non-responsive, uni- or bilateral ear droop with a head tilt, fever and epiphora chronic weight-loss and wasting, and can result in otitis interna and meningitis* *Tympanic bullae filled with a fibrinosupporative to caseous exudate*

Reproductive disease	Other disease
(Endo)metritis *Seminal vesiculitis => contaminated sperm => increasing the number of insemination required before conception* *Abortion*	*Infectious Keratoconjunctivitis* *Abscesses* *Meningitis* *Polyserositis and pericarditis*

Additional Information/Literature

S. Bürki, J. Frey, and P. Pilo (2015). Virulence, persistence and dissemination of *Mycoplasma bovis*. Vet Microbiol 179:15–22.

Funk, L., O'Connor, A. M., Maroney, M., Engelken, T., Cooper, V. L., Kinyon, J., & Plummer, P. (2009). A randomized and blinded field trial to assess the efficacy of an autogenous vaccine to prevent naturally occurring infectious bovine keratoconjunctivis

(IBK) in beef calves. Vaccine *27*(34), 4585-4590.

El-Jakee, J., Mohamed, K. F., & Marouf, S. A. (2011). Preparation of autogenous bivalent vaccine for *M. bovis* and *M. bovigenitalium* in Egypt. Life Science Journal *8*(4), 338-343.

Maunsell, F. P., Donovan, G. A., Risco, C., & Brown, M. B. (2009). Field evaluation of a *Mycoplasma bovis* bacterin in young dairy calves. Vaccine *27*(21), 2781-2788.

F.P. Maunsell, A.R. Woolums, D. Francoz, R.F. Rosenbusch, D.L. Step, D.J. Wilson, and E.D. Janzen (2011). *Mycoplasma bovis* Infections in Cattle. J Vet Intern Med; 25:772-783.

2.2.3.2 Autogenous vaccines against Moraxella bovis and Moraxella bovoculi - infections in cattle

Disease/Indication
Infectious Bovine Keratoconjunctivitis (IBK), Pink Eye Disease

Pathogen/Antigen(s)
Moraxella bovis
Moraxella bovoculi

Frequency/Importance
Infectious bovine keratoconjunctivitis (IBK) is a common and important disease of calves and adult cattle. Moreover, it is considered as one of the most important production-limiting diseases of pre-weaned beef and dairy calves.

Clinical picture and Losses
The clinical signs of IBK include lacrimation, photophobia, corneal oedema, ocular pain, corneal ulceration, and the potential for vision loss.

The earliest clinical signs are photophobia, blepharospasm, and epiphora; later, the ocular discharge may become mucopurulent. Conjunctivitis, with or without varying degrees of keratitis, is usually present.

Calves with IBK lesions have a decreased weaning weight by 15–30 lb compared with unaffected calves.

Additional Information/Literature
J. N. Cullen, C. Yuan, S. Totton, R. Dzikamunhenga, J. F. Coetzee1, N. da Silva, C. Wang, and A. M. O'Connor (2016). A systematic review and meta-analysis of the antibiotic treatment for infectious bovine keratoconjunctivitis: an update. Animal Health Research Reviews 17:60–75.

Davidson, H. J., & Stokka, G. L. (2003). A field trial of autogenous *Moraxella bovis* bacterin administered through either subcutaneous or subconjunctival injection on the development of keratoconjunctivitis in a beef herd. The Canadian Veterinary Journal *44*(7), 577.

Funk, L., O'Connor, A. M., Maroney, M., Engelken, T., Cooper, V. L., Kinyon, J., & Plummer, P. (2009). A randomized and blinded field trial to assess the efficacy of an autogenous vaccine to prevent naturally occurring infectious bovine keratoconjunctivis (IBK) in beef calves. Vaccine *27*(34), 4585-4590.

2.2.3.3 Autogenous vaccines against Mycoplasma bovoculi - infections in cattle

Disease/Indication
Infectious bovine keratoconjunctivitis (IBK), pinkeye disease

Pathogen/Antigen(s)
Mycoplasma bovoculi

Frequency/Importance
Infectious bovine keratoconjunctivitis (IBK) is a highly contagious disease affecting cattle worldwide that can spread rapidly within a herd through direct contact, nasal or ocular discharges and via insect vectors. Considerable economic impact has been attributed to IBK, particularly due to reduced weight gain in calves at weaning and high costs associated with antibiotic treatment. Besides *Moraxella bovis* and *Moraxella bovoculi, Mycoplasma bovis* and *Mycoplasma bovoculi* might also be involved in clinical cases of IBK.

Clinical picture and Losses
IBK can produce ocular discharge, epiphora, mild conjunctivitis and corneal opacity, resulting in transitory blindness in most cases. However, IBK outbreaks may result in more severe clinical signs, including infection of the cornea that may lead to ulceration and perforation of the eye.

Additional Information/Literature
Xavier Fernández-Aguilar, Luca Rossi, Óscar Cabezón, Andrea Giorgino, Isis Victoriano Llopis, Joachim Frey, Jorge Ramón López-Olvera: Infectious keratoconjunctivitis and occurrence of Mycoplasma conjunctivae and Chlamydiaceae in small domestic ruminants from Central Karakoram, Pakistan. Vet Rec 2017; 181(9):237.

Wanglong Zheng, Elizabeth Porter, Lance Noll, Colin Stoy, Nanyan Lu, Yin Wang, Xuming Liu, Tanya Purvis, Lalitha Peddireddi, Brian Lubbers, Gregg Hanzlicek, Jamie Henningson, Zongping Liu, Jianfa Bai: A multiplex real-time PCR assay for the detection and differentiation of five bovine pinkeye pathogens. J Microbiol Methods 2019; 160:87-92.

2.2.3.4 Autogenous vaccines against Mycoplasma bovirhinis - infections in cattle

Disease/Indication
Mycoplasma bovirhinis infections as part of the bovine respiratory disease complex

Pathogen/Antigen(s)
Mycoplasma bovirhinis

Frequency/Importance
Mycoplasma bovirhinis can be isolated from the respiratory tract of healthy and sick cattle as well as buffaloes and is a commensal of the upper respiratory tract. It is often associated with respiratory infections caused by other bacterial agents like *Mycoplasma bovis, Pasteurella multocida, Histophilus somni* or viruses like Bovine Respiratory Syncytial Virus.

Clinical picture and Losses
Mycoplasma bovirhinis can be associated with respiratory disease symptoms like coughing and nasal discharge. It could be isolated from lungs with different forms of pneumonia. In general, the bacterium plays a role in the bovine respiratory disease complex, which is one of the most important diseases in cattle.

Additional Information/Literature
J. W. Allen et al. (1992). Changes in the bacterial flora of the upper and lower respiratory tracts and bronchoalveolar lavage differential cell counts in feedlot calves treated for respiratory disease. Can J Vet Res 56(3):177-183.

V. Bitsch et al. (1976). A microbiological study of pneumonic calf lungs. Acta vet scand 17:32-42.

M. S. Hazelton et al. (2020). Mycoplasma bovis and other Mollicutes in replacement dairy heifers from Mycoplasma bovis-infected and uninfected herds: A 2-year longitudinal study. J Dairy Sci 103:11844-11856.

K. Hirose et al. (2003). Isolation of Mycoplasmas from nasal swabs of calves affected with respiratory diseases and antimicrobial susceptibility of their isolates. J Vet Med B Infect Dis Vet Public Health 50(7):347-51

2.2.3.5 Autogenous vaccines against Histophilus somni - infection in cattle

Disease/Indication
Bronchopneumonia

Pathogen/Antigen(s)
*Histophilus somni (*previously known as *Haemophilus somnus)*

Frequency/Importance
Cattle 6 months to 2 years of age tend to be most frequently affected.
Known antibiotic resistance.

Clinical picture and Losses
Pneumonia associated with environmental and stress factors such as shipping, co-mingling, as well as concurrent or predisposing viral or bacterial infections.
Fever, dyspnoea, nasal and ocular discharge, possible septicaemia when *H. somni* reaches blood vessels. Nervous system may also be affected (thromboembolic meningoencephalitis) Death can occur within a day after the onset of clinical signs.

Clinical picture is an acute to subacute bronchopneumonia associated or not with pleuritis.

Additional Information/Literature
Bednarek, D., Szymańska-Czerwińska, M., & Dudek, K. (2012). Bovine respiratory syndrome (BRD) etiopathogenesis, diagnosis and control. A Bird's-Eye View of Veterinary Medicine. Dr. Carlos C. Perez-Marin (Ed.), 363-378.

Shirbroun RM. Histophilus somni: Antigenic and Genomic Changes Relevant to Bovine Respiratory Disease. Vet Clin North Am Food Anim Pract. 2020;36(2):279-295. DOI 10.1016/j.cvfa.2020.02.003.

2.2.3.6 Autogenous vaccines against Dermatitis digitalis/Mortellaro - infection in cattle

Disease/Indication
Mortellaro's disease, Dermatitis digitalis

Pathogen/Antigen(s)
Treponema spp. associated to other bacteria such as *Bacteroides* spp., *Fusobacterium necrophorum, Dichelobacter nodosus.*

Frequency/Importance
Frequent to very frequent cause of contagious dermatosis of digital skin in cattle. Most frequent in housed dairy cows.

Additional Information/Literature
Smith, B. P.; Metre, D.V.; Pusterla, N. (ed.) (2019). Large Animal Internal Medicine. 6th ed., Elsevier.

2.2.3.7 Autogenous vaccines against Salmonella - infection in cattle

Disease/Indication
Salmonellosis

Pathogen/Antigen(s)
Most frequent strains*: Salmonella* Dublin*, Salmonella* Typhimurium, a variety of other serovars can occur.

Frequency/Importance
Increasing prevalence in recent year
Long-lasting infection – carrier.
One Health aspects: Zoonotic importance; Antibiotic-resistant strains.

Clinical picture and Losses

Peracute	Acute	Chronic case
New-born calves with inadequate colostral immunity	**Adult with poor immunity condition**	**Clinical form**
Fever; diarrhoea (yellow with or without flecks of blood and mucus); rapid dehydration, prostration and death occurring within 24-48 hours due to fulminating septicaemia. Mortality high.	Fever followed by anorexia, depression and diarrhoea with blood, mucus, fibrinous casts, and/or shreds of intestinal mucosa Drop milk production Abortion	After the acute form, intermittent fever with watery diarrhoea Dehydration may occur, loss of weight
8-10 days old calves		**Carrier form**
Fever, pneumonia/septicaemia, with or without diarrhoea. Arthritis and meningitis. Morbidity is high as is mortality in untreated calves.		Acute cases that recover may become carriers that shed *Salmonella* for varying periods (e.g., *S.* Typhimurium from 3 to 6+ months versus *S.* Dublin = lifelong carriers). Carrier animals can develop clinical disease whenever the immune function is compromised

Additional Information/Literature

Barrow, P.; Methner, U. (2013). Salmonellosis in domestic animals. 2 ed., CABI Publ., UK (Chapter 22: Vaccination against *Salmonella* infections in food animals: rationale, theoretical and practical applications). DOI 10.1079/9781845939021.0000

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Hermesch, D. R., Thomson, D. U., Loneragan, G. H., Renter, D. R., & White, B. J. (2008). Effects of a commercially available vaccine against *Salmonella enterica* serotype Newport on milk production, somatic cell count, and shedding of *Salmonella* organisms in female dairy cattle with no clinical signs of salmonellosis. American Journal of Veterinary Research *69*(9), 1229-1234

Holubek, R.; Selbitz, H.-J. (2014). Impfungen gegen Rindersalmonellose langfristig durchführen (Carry out vaccinations against bovine salmonellosis in the long term). Prakt. Tierarzt 95: 1038-1045

2.2.3.8 Autogenous vaccines against Pasteurella multocida - infection in cattle

Disease/Indication
Bovine Pasteurellosis (mainly serogroup A), Haemorrhagic Septicaemia (serogroups B and E), Fatal Fibrinous Peritonitis in Calves (serogroup F), Bronchopneumonia

Pathogen/Antigen(s)
Pasteurella multocida
Pathogenic Gram-negative bacterium that has been classified into three subspecies (subsp. *multocida, septica, gallicida),* five capsular serogroups (A, B, D, E, F) and 16 serotypes.

Frequency/Importance
P. multocida is one of the primary bacterial pathogens associated with the clinical syndromes defining Bovine Respiratory Disease (BRD) complex including enzootic neonatal calf pneumonia and beef cattle pneumonia (shipping fever) worldwide. Furthermore, *P. multocida* serogroup B and E might cause fatal outbreaks of Haemorrhagic Septicaemia (HS) in domestic and wild ruminants. Recently, serogroup F was found to cause fatal cases of peritonitis in calves.
Known antibiotic resistance.

Clinical picture and Losses
P. multocida serogroup A causes both enzootic calf pneumonia of young dairy calves and shipping fever of weaned beef cattle. Lung lesions consist of an acute to subacute bronchopneumonia that may or may not have an associated pleuritis.
P. multocida serogroups B and E might cause HS in both, domestic and wild ruminants. HS can be defined as an acute, fatal and septicaemic disease often leading to sudden death with no clinical signs visible. HS is a WOAH (World Organisation for Animal Health, founded as OIE)-Listed Disease in force in 2021, and is known as a primary pasteurellosis with 100% mortality in infected animals in endemic areas.

P. multocida serogroup F was recently found to cause cases of fatal peritonitis in calves.

Bovine respiratory syndrome, pneumonia associated with environmental and stress factors such as shipping, co-mingling, as well as concurrent or predisposing viral or bacterial infections.

Clinical picture is an acute to subacute bronchopneumonia associated or not with pleuritis.

Additional Information/Literature

Bednarek, D., Szymańska-Czerwińska, M., & Dudek, K. (2012). Bovine respiratory syndrome (BRD) etiopathogenesis, diagnosis and control. A Bird's-Eye View of Veterinary Medicine. Dr. Carlos C. Perez-Marin (Ed.) 363-378

S.M. Dabo, J.D. Taylor, and A.W. Confer (2008). *Pasteurella multocida* and bovine respiratory disease. Animal Health Research Reviews 8:129-150

Kutzer, P. et al. (2021). Re-emergence and spread of haemorrhagic septicaemia in Germany – The wolf as a vector? Microorganisms 9(9), 1999.
DOI 10.3390/microorganisms9091999

Otomaru, K., Kubota, S., & Tokimori, M. (2015). Maternally and naturally acquired antibodies to *Pasteurella multocida* in Japanese Black calves. Pak. Vet. J *35*(108), e110

S.B. Shivachandra, K.N. Viswas, and A.A. Kumar (2011). A review of hemorrhagic septicemia in cattle and buffalo. Animal Health Research Reviews; 12:67–82

2.2.3.9 Autogenous vaccines against Trueperella - infection in cattle

Disease/Indication
Abscesses, mastitis, (endo) metritis and sporadic abortion, seminal vesiculitis

Pathogen/Antigen(s)
Trueperella pyogenes. (formerly *Arcanobacterium pyogenes*)

Frequency/Importance
Unusual pathogen, could be a secondary invader

Clinical picture and Losses
Trueperella pyogenes is a part of the biota of skin and mucous membranes of the upper respiratory, gastrointestinal, or urogenital tracts of animals, but also, an opportunistic pathogen. *T. pyogenes* causes a variety of purulent infections, such as metritis, mastitis, pneumonia, and abscesses, mastitis in heifers and dry cows.

Pain and fever. Profuse, foul-smelling, purulent exudate. Mastitis due to *T. pyogenes* is common among dry cows and heifers living in wet areas. The spread into the herd is mainly caused by the fly *Haematobia irritans*.

Treatment is often unsuccessful, and the infected quarter is usually lost to production. High morbidity and cows with abscesses could not recover and usually should be slaughtered.

Sporadic abortion at any stage of pregnancy. Rarely, the incidence in a herd may reach epizootic levels. The bacterium is present in the nasopharynx of many healthy cows and in abscesses. Endometritis and placentitis are described, which are diffuse with a reddish brown to brown colour. The foetus is usually autolyzed, with fibrinous pericarditis, pleuritis, or peritonitis possible.

Additional Information/Literature
Machado VS, Bicalho ML, Meira Junior EB, et al. Subcutaneous immunization with inactivated bacterial components and purified protein of *Escherichia coli*, *Fusobacterium necrophorum* and *Trueperella pyogenes* prevents puerperal metritis in Holstein dairy cows. PLoS One. 2014;9(3): e91734. Published 2014 Mar 17. DOI 10.1371/journal.pone.0091734.

2.2.3.10 Autogenous vaccines against Streptococcus spp. (mastitis) - infection in cattle

Disease/Indication
Mastitis

Pathogen/Antigen(s)
Streptococcus spp.
S. uberis (environmental pathogen), *S. dysgalactiae* (environmental pathogen), *S. agalactiae* (cow-associated pathogen)

Frequency/Importance
Streptococcus spp. is one of the most common bacteria involved in bovine mastitis.
S. agalactiae is the cause of subclinical mastitis in dairy cattle leading to huge economic loss. *S. agalactiae* may be transmitted from udder to udder in many ways.
Known antibiotic resistance.

Clinical picture and Losses

Acute mastitis	Subclinical mastitis
Fever, pain	No obvious clinical sign nor visible changes to the composition of the milk. Increase of somatic cell count
Abnormal milk consisting of white to yellow clots and flakes	
Reduction or stopping of the milk production	Reduction of yield
	Source of infection for the other cows, becoming subclinical or clinical themselves

Additional Information/Literature
Ismail ZB. Mastitis vaccines in dairy cows: Recent developments and recommendations of application. Vet World 2017;10(9):1057-1062.
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Date accessed: 08 June 2020. DOI 10.21640/ns.v2i4.207

2.2.3.11 Autogenous vaccines against Papillomatosis in cattle

Disease/Indication
Bovine Papillomatosis

Pathogen/Antigen(s)
Bovine Papilloma Virus (BPV) belonging to the family *Papillomaviridae* with the genera *Deltapapillomavirus* (BPV- 1, 2), *Epsilonpapillomavirus* (BPV- 5), *Xipapapillomavirus* (BPV- 3,4,6), *Dyoxipapillomavirus* (BPV-7). Most of the papillomaviruses are species-specific, BPV-1 and BPV-2 also infect horses (equine sarcoid). They have a tropism for epithelial and mucous tissues. The immunity against papillomaviruses is type-specific.

Frequency/Importance
Bovine Papillomatosis is a worldwide, sporadic occurring disease.

Clinical picture and Losses
Papillomas and fibropapillomas (BPV-1, BPV-2) in animals less than two years of age, persisting papillomas in older animals. The warts are most numerous on the head, neck, shoulder and brisket, but also on the abdomen, back, legs, anal and genital area, udder and teats.

Additional Information/Literature
Aydin, H.; Gelen, V.; Sengül, E.; Yildirim, S. (2020). Immunological effects of autogenous vaccine administration in cattle with cutaneous papillomatosis. Acta Vet Eurasia 46: 98-103. DOI 10.5152/actavet.2020.20002

Borzachiello, G.; Roperto, F. (2008). Bovine papilloma viruses, papillomas and cancer in cattle. Vet. Res. 39: 45. DOI:10.1051/vetres:2008022

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Terziev, G.; Roydev, R.; Kalkanov, I.; Borissov, I.; Dinev, I. (2015). Papillomatosis in heifers - comparative studies on surgical excision and autogenous vaccines therapies. Trakia J. Sci. 13: 274-279. DOI 10.15547/tjs.2015.s.02.061

2.2.3.12 Autogenous vaccines against Bovine Respiratory Coronaviruses in cattle

Disease/Indication

Bovine Respiratory Coronavirus infection
Part of the Bovine Respiratory Disease Complex

Pathogen/Antigen(s)

Bovine Coronaviruses (BCoV) (*Coronaviridae*)

Frequency/Importance

Bovine Coronavirus (BCoV) causes respiratory and enteric infections in cattle and wild ruminants. They are spread all over the world. It is a pneumoenteric virus that infects the upper and lower respiratory tract and intestine. It is shed in faeces and nasal secretions and might also infect the lungs. BCoV is the cause of 3 distinct clinical syndromes in cattle: (1) calf diarrhoea, (2) winter dysentery with haemorrhagic diarrhoea in adults, and (3) respiratory infections in cattle of various ages including the bovine respiratory disease complex or shipping fever of feedlot cattle which is one of the most important diseases in cattle.

Clinical picture and Losses

BCoV are precursors for bacterial and other viral secondary infections. The virus thus plays an important role in the bovine respiratory disease complex, which is one of the most important diseases in cattle. BCoV are transmitted through direct contact.

Additional Information/Literature

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2.2.3.13 Autogenous vaccines against Influenza D virus - infections in cattle

Disease/Indication
Influenza D virus infection
Part of the Bovine Respiratory Disease Complex

Pathogen/Antigen(s)
Influenza D virus (*Orthomyxoviridae*)

Frequency/Importance
Influenza D virus is a newly described virus of cattle, pigs and small ruminants first detected in North America during 2011. Cattle have been shown to be the main viral reservoir and mounting evidence indicates that infection with influenza D virus may contribute to the development of bovine respiratory disease which is one of the most important diseases of cattle worldwide.

Clinical picture and Losses
Cattle are considered a natural reservoir for influenza D virus and can also contract a severe respiratory infection with high fever. Influenza D virus is a precursor for bacterial and other viral secondary infections. The virus thus plays an important role in the bovine respiratory disease complex, which is one of the most important diseases in cattle. Influenza D virus is transmitted through direct contact.

Additional Information/Literature
Ducatez, M. F., Pelletier, C, & Meyer, G. (2015). Influenza D virus in cattle, France, 2011–2014. Emerging Infectious Diseases, 21, 368-371.

Flynn, O., Gallagher, C., Mooney, J., Irvine, C, Ducatez, M., Hause, B., & Ryan, E. (2018). Influenza D virus in cattle, Ireland. Emerging Infectious Diseases, 24, 389-391.

Hause, B. M., Collin, E. A., Liu, R., Huang, B., Sheng, Z., Lu, W., Li, F. (2014). Characterization of a novel influenza virus strain in cattle and swine: proposal for a new genus in the Orthomyxoviridae family. mBio 2014 Mar-Apr: 5(2): e00031-14. DOI 10.1128/mBio.00031-14

2.2.4 Autogenous Vaccines for Sheep and Goats

2.2.4.1 Autogenous vaccines against Campylobacter spp. - infection in small ruminants

Disease/Indication
Campylobacteriosis

Pathogen/Antigen(s)
Campylobacter jejuni and *C. fetus* subsp. *fetus* (sheep)

Frequency/Importance
Gastrointestinal tract as long-term reservoir for *Campylobacter* spp. High zoonotic potential (infection acquired by undercooked contaminated food).

Clinical picture and Losses
Abortion in late pregnancy (12th week) or full-term birth of dead or weakly lamps/kids based on placentitis. In necropsy, aborted or stillborn foetuses characterized by serosanguinous fluid throughout the abdomen and thorax, focal liver lesions and bronchopneumonia.

Additional Information/Literature
Garcia, M. M., Lior, H., Stewart, R. B., Ruckerbauer, G. M., Trudel, J. R., & Skljarevski, A. Isolation, characterization, and serotyping of *Campylobacter jejuni* and *Campylobacter coli* from slaughter cattle. Applied and Environmental Microbiology. 1985; 49(3), 667–672.

Mearns, R. (2007). Other infections causes of abortion. In I. Aitken (Ed.), Diseases of Sheep (4th Edition, pp. 127–136). Wiley-Blackwell.

Wu Z, Sippy R, Sahin O, et al. Genetic diversity and antimicrobial susceptibility of *Campylobacter jejuni* isolates associated with sheep abortion in the United States and Great Britain. J Clin Microbiol. 2014;52(6):1853-1861. DOI 10.1128/JCM.00355-14

Shaokat, A., Zhihui, Z., Gao, Z., Jin, ZK, Pan, ZY. Reproductive problems in small ruminants (Sheep and goats): A substantial economic loss in the world. Large Animal Review. 2019; 25(6), 215-223.

2.2.4.2 Autogenous vaccines against Clostridium perfringens - infection in goats

Disease/Indication
Clostridiosis

Pathogen/Antigen(s)
Clostridium perfringens: Five toxinotypes (A, B, C, D, E), Four major toxins (alpha, beta, epsilon, iota), >15 toxins such as perfringolysin O (*pfo*), enterotoxin (*cpe*), beta2 toxin (*cpb*2)

Frequency/Importance
Type D, most common form. The acute form: in young unvaccinated animals; the subacute form: in adult goats. Enterotoxaemia with *C. perfringens* type A (*cbp*2+) in goat kids.

Clinical picture and Losses
C. perfringens Type D characterized by sudden death or signs including blindness, opisthotonos, convulsions, bleating, frothing by the mouth, in **subacute form** in goats additionally indicated with haemorrhagic diarrhoea, in **chronic form** identified with profuse, watery diarrhoea. In lamps, *C. perfringens* Type A induces the rare acute enterotoxaemia **yellow lamp disease** with generalized icterus and enlarged, pale, and friable liver and spleen.

Additional Information/Literature
Pawaiya, R., Gururaj, K., Gangwar, N., Singh, D., Kumar, R. and Kumar, A. (2020). The Challenges of diagnosis and control of enterotoxaemia caused by *Clostridium perfringens* in small ruminants. Advances in Microbiology. 2020; 10: 238-273.

Uzal, FA, Kelly, WR, Morris, WE (2004). The pathology of experimental *Clostridium perfringens* type D enterotoxemia in sheep. J Vet Diagn Invest 16:403-411.

2.2.4.3 Autogenous vaccines against Dichelobacter nodosus, Fusobacterium necrophorum and Treponema spp. - infection in sheep

Disease/Indication
Contagious ovine digital dermatitis (CODD)
Footrot

Pathogen/Antigen(s)
Dichelobacter nodosus; virulent and benign form; serogroups A-I, M
Fusobacterium necrophorum
Treponema spp. especially *T. medium, T. phagedenis, T. pedis*

Clinical picture and Losses
CODD caused by *Dichelobacter nodosus*, *Fusobacterium necrophorum* and *Treponema* spp. is characterized by severe lameness associated with initial inflammation at the coronary band and interdigital space with red, moist interdigital skin and white/grey pasty exudate, followed by progressive separation of the hoof capsule from the underlying tissue. In **footrot** caused by *Dichelobacter nodosus* and *Fusobacterium necrophorum*, separation of the hoof horn from the sensitive tissue of the claw with a grey scum presents in the resulting cavity.

Additional Information/Literature
Duncan JS, Angell JW, Carter SD, Evans NJ, Sullivan LE, Grove-White DH. (2014). Contagious ovine digital dermatitis: an emerging disease. Vet J. 201(3):265-268.

Crosby-Durrani HE, Clegg SR, Singer E, et al. (2016). Severe Foot Lesions in Dairy Goats Associated with Digital Dermatitis Treponemes. J Comp Pathol. 154(4):283-296.

M.B. Allworth. (2013). Challenges in ovine footrot control. Small Rumin Res. 118(01).

Gelasakis AI, Kalogianni AI, Bossis I. (2019). Aetiology, Risk Factors, Diagnosis and Control of Foot-Related Lameness in Dairy Sheep. Animals (Basel). 9(8):509.

2.2.4.4 Autogenous vaccines against E. coli - infection in small ruminants

Disease/Indication
Colibacillosis

Pathogen/Antigen(s)
Enterotoxigenic E. coli (ETEC)

Frequency/Importance
In neonates, ETEC infection occurs within the first 72h of life.

Clinical picture and Losses
Gastroenteritis characterized in semifluid, yellow to grey diarrhoea and /or **septicaemia** between 2nd and 6th week of age with nerval symptoms such as incoordination, head pressing, circling and the appearance of blindness and swollen and painful joints. In acute enteric form, mortality may be as high as 75%. Additionally, *E. coli* also may cause **cystitis** and **pyelonephritis** in small ruminants.

Additional Information/Literature
Underwood, W. J., Blauwiekel, R., Delano, M. L., Gillesby, R., Mischler, S. A., & Schoell, A. (2015). Biology and Diseases of Ruminants (Sheep, Goats, and Cattle). Laboratory Animal Medicine, 623–694. DOI 10.1016/B978-0-12-409527-4.00015-8

Wieler, L. (2021). *Escherichia-coli*-Diarrhö und Septikämie. In: Bostedt, H.; Ganter, M.; Hiepe, T. (Hrsg.): Klinik der Schaf- und Ziegenkrankheiten. 2. Aufl., Georg Thieme Verl. Stuttgart, 300-301.

2.2.4.5 Autogenous vaccines against Helcococcus ovis - infection in small ruminants

Disease/Indication
Helcococcus ovis-infection

Pathogen/Antigen(s)
Helcococcus ovis

Clinical picture and Losses
Pleuritis and bronchopneumonia is described in ewe lambs. Subclinical mastitis together with *Staphylococcus* spp. can be observed.

Additional Information/Literature
Collins MD, Falsen E, Foster G, et al. (1999). *Helcococcus ovis* sp. nov., a gram-positive organism from sheep. International Journal of Systematic Bacteriology. 1999 Oct;49 Pt 4:1429-1432. DOI 10.1099/00207713-49-4-1429.

García A, Risco D, Benítez JM, et al. (2012). *Helcococcus ovis* isolated from a goat with purulent bronchopneumonia and pulmonary abscesses. J Vet Diagn Invest. 24(1):235-237. DOI 10.1177/1040638711425950

Kutzer P, Schulze C, Engelhardt A, Wieler LH, Nordhoff M. (2008). *Helcococcus ovis*, an emerging pathogen in bovine valvular endocarditis. J Clin Microbiol. 46(10):3291-3295. DOI 10.1128/JCM.00867-08.

2.2.4.6 Autogenous vaccines against Mannheimia haemolytica - infection in small ruminants

Disease/Indication
Mannheimiosis, Respiratory Infection, Bronchopneumonia

Pathogen/Antigen(s)
Mannheimia haemolytica
12 serotypes using capsular antigens (A1, A2, A5-A9, A12-A14, A16, A17)

Frequency/Importance
The opportunistic pathogen particularly inhabits the nasopharynx and tonsils and can affect sheep and goats of all ages. Acute respiratory disease is common in young animals in high stress phase.

Clinical picture and Losses
M. haemolytica serotype A2 causes pneumonic pasteurellosis in sheep and goats. In acute cases, the animals show depression, lethargy, inappetence, elevated temperature and rapid shallow breathing accompanied by profuse mucopurulent nasal and ocular discharges. At necropsy, the bronchopneumonia has a cranioventral lung distribution.

Additional Information/Literature
Abbas, G. et al. (2019). *Mannheimia haemolytica* infection in small ruminants: a review. Advances in Zoology and Botany. 7(1): 1-10.

Abdelsalam E.B. (2008). A review on pneumonic pasteurellosis (respiratory mannheimiosis) with emphasis on pathogenesis, virulence mechanisms and predisposing factors. Bulg. J. Vet. Med. 11(3):139-160.

2.2.4.7 Autogenous vaccines against Pasteurella multocida - infection in small ruminants

Disease/Indication
Pasteurellosis, Bronchopneumonia, Haemorrhagic Septicaemia

Pathogen/Antigen(s)
Pasteurella multocida: five serogroups A, B, D, E and F (capsule structure) and 16 serotypes (LPS).

Frequency/Importance
Common infection in young animals around weaning.

Clinical picture and Losses
Acute pasteurellosis characterized by fever, cough, nasal and eye discharge as well as diarrhoea associated with *P. multocida* type A and D, commonly in sheep. In necropsy, animals show haemorrhagic bronchopneumonia with cranioventral lung distribution accompanied by pleuritis and pericarditis. Type B and E can infect goats based on haemorrhagic septicaemia.

Additional Information/Literature
Dabo, S.M. Taylor, J.D., Confer, A.W. (2007). *Pasteurella multocida* and bovine respiratory disease. Anim. Health Res. Rev. 8, 129-150.

Ozyildiz, Z., Tel, O.Y., Yilmaz, R., Ozsoy, S.Y., Keskin, O. (2013). Pathological and microbiological investigations of pneumonic pasteurellosis in sheep. J. Fac. Vet. Med. Univ. Kafkas. 19, 103-108.

Sunder, J., Kumar, A.A. (2001). Studies on toxigenic strains of *Pasteurella multocida* of goat origin Indian. Vet. J., 78: 184-188.

Watson, P.J., Davis, R.L. (2002). Outbreak of *Pasteurella multocida* septicaemia in neonatal lambs. Vet. Record. 151, 420-422.

2.2.4.8 Autogenous vaccines against Bibersteinia trehalosi - infection in small ruminants

Disease/Indication
Pasteurellosis (Bibersteiniosis), Pneumonia

Pathogen/Antigen(s)
*Bibersteinia (*formerly *Pasteurella) trehalosi*; four known serotypes (T3, T4, T10, T15).

Frequency/Importance
Normal inhabitant of the tonsils and nasopharynx of sheep and goats affects four- to nine-month-old lambs and kids and causes septicaemia leading to high mortality rates. Also, animals in all ages can get pneumonia.

Clinical picture and Losses
Septicaemic, acute and chronic pneumonic pasteurellosis in sheep and goats, resulting in death. Lambs show persistent respiratory lesions that remain in subclinical form and are only detected at slaughtering.

Additional Information/Literature
Gonzalez, J., Lacasta, D., Ferrer, L., Figueras, L., Abadie, G., & de las Heras, M. (2017). *Mannheimia haemolytica* and *Bibersteinia trehalosi* serotypes isolated from lambs with ovine respiratory complex in Spain. Journal of the Hellenic Veterinary Medical Society 64(3), 177-182.

Quinn, P. J., Markey, B. K., Leonard, F. C., FitzPatrick, E. S., Fanning, S. and Hartigan, P. J. (2011). *Pasteurella* species, *Mannheimia haemolytica* and *Bibersteinia trehalosi*. In: Veterinary Microbiology and Microbial Disease. 2nd edition. Blackwell Science Ltd., Oxford, UK. 2011. 300–308.

2.2.4.9 Autogenous vaccines against Staphylococcus aureus - infection in small ruminants

Disease/Indication
Mastitis

Pathogen/Antigen(s)
Staphylococcus aureus

Frequency/Importance
Incidence more in sheep; but in both animal species relatively infrequent, generally more than in cows.

Clinical picture and Losses
Peracute/acute mastitis dominated by depression, initial fever, dehydration, anorexia and swollen, discoloured gland which may be followed to hard, fibrotic consistency (chronic) with flake-containing, purulent milk in sheep and goats.

Additional Information/Literature
Attili, A. *et al*. (2016). Clinical evaluation of the use of enrofloxacin against *Staphylococcus aureus* clinical mastitis in sheep. Small Rumin. Res. 136, 72-77.

Menzies PI, Ramanoon SZ. (2001). Mastitis of sheep and goats. Vet Clin North Am Food Anim Pract 17(2):333-vii. DOI 10.1016/s0749-0720(15)30032-3

Merz, Axel; Stephan, Roger; Johler, Sophia (2016). *Staphylococcus aureus* isolates from goat and sheep milk seem to be closely related and differ from isolates detected among bovine milk. Frontiers in Microbiology, 7:319.

Rainard, P, Foucras, G, Fitzgerald, JR, Watts, JL, Koop, G, Middleton, JR. (2018). Knowledge gaps and research priorities in *Staphylococcus aureus* mastitis control. Transbound Emerg Dis 65 (Suppl. 1): 149-165. DOI 10.1111/tbed.12698.

2.2.4.10 Autogenous vaccines against Morel´s Disease in small ruminants

Disease/Indication
Morel´s Disease (abscess disease)

Pathogen/Antigen(s)
Staph. aureus subsp. anaerobius

Frequency/Importance
Morel's disease (MD) is a non-fatal, contagious disease of sheep and goats as primary hosts. MD is caused by *Staphylococcus aureus subsp. anaerobius*. The disease is endemic in nature with high morbidity rate. Once introduced into a flock, MD is very difficult to control because of its poor response to treatment, its ability to persist in the environment and the limitations in detecting sub-clinically infected animals. Considerable economic losses due to MD in the sheep and goats' industry are reported from countries where they prevail (mainly Africa, Asia, and Europe). Losses are caused by condemnation and downgrading of carcasses and skin in abattoirs as well as reduction in reproductive efficiency, wool growth, meat, and milk production.

Clinical picture and Losses
MD shows similar clinical symptoms as they occur in caseous lymphadenitis (CLA): they are characterized by abscess formation adjacent to or inside lymph nodes. In MD, abscesses are formed near or inside superficial lymph nodes, while in CLA abscesses are formed only inside both superficial and visceral lymph nodes. As MD is having a much shorter (2-3 weeks) incubation period compared to CLA (2-6 months), it is expected to be more endemic, and outbreaks occur much faster.

Additional Information/Literature
Elhassan M. A. Saeed and Khalid B. Alharbi: Morel's Disease and Caseous Lymphadenitis: a Literature Review with Special Reference to Saudi Arabia. IOSR Journal of Agriculture and Veterinary Science (IOSR-JAVS) 2014, 7(5):76-86.

O Szaluś-Jordanow, J Kaba, M Czopowicz, L Witkowski, M Nowicki, D Nowicka, I Stefańska, M Rzewuska, M Sobczak-Filipiak, M Binek, T Frymus: Epidemiological features of Morel's disease in goats. Pol J Vet Sc. 2010, 13(3):437-45.

2.2.4.11 Autogenous vaccines against Streptococcus spp. - infection in small ruminants

Disease/Indication
Streptococcosis, Mastitis

Pathogen/Antigen(s)
Streptococcus (Sc.) agalactiae, Sc. dysgalactiae, Sc. equi subsp. *zooepidemicus*, *Sc. uberis*

Frequency/Importance
Sc. equi subsp. *zooepidemicus:* part of the normal flora of the respiratory and urogenital tracts of equines; *Sc. dysgalactiae* in 1-3-week-old lambs.

Clinical picture and Losses
Streptococcus spp. (commonly *Sc. dysgalactiae* and *Sc. uberis)* may cause individual **mastitis** or an outbreak in flocks. *Sc. agalactiae* leads to acute mastitis in sheep (high morbidity and rapid reduction in milk production) or subclinical mastitis of long duration (high counting of somatic cells). Udders can swell and become warm (affected blood: Blue bag). *Sc. dysgalactiae* can also cause **polyarthritis** in goats and lambs.

Additional Information/Literature
Steward KF, Robinson C, Holden MTG, et al. (2017). Diversity of *Streptococcus equi* subsp. *zooepidemicus* strains isolated from the Spanish sheep and goat population and the identification, function and prevalence of a novel arbutin utilisation system. Vet Microbiol 207:231-238.

Delia Lacasta, Luís M. Ferrer, Juan J. Ramos, Araceli Loste, Juan P. Bueso (2008). Digestive pathway of infection in *Streptococcus dysgalactiae* polyarthritis in lambs. Small Ruminant Research 78(1-3); 202-205

Zdragas, A., Tsakos, P., Kotzaminidis, C., Anatoliotis, K. and Tsaknakis, I. (2017). Outbreak of mastitis in ewes caused by *Streptococcus agalactiae*. Journal of the Hellenic Veterinary Medical Society 56(2); 114-121.

2.2.4.12 Autogenous vaccines against Mycoplasma spp. - infection in small ruminants

Disease/Indication
Atypical Pneumonia

Pathogen/Antigen(s)
Mycoplasma (M.) ovipneumoniae, *M. arginini*, *M. mycoides* subsp. *capri*, *M. agalactiae, Mycoplasma capricolum* subsp*. capripneumoniae, M. putrefaciens*

Frequency/Importance
Mycoplasma spp. affects animals in all ages. Possible Persistence for >1 year after clinical recovery of infected animals (main reservoir)

Clinical picture and Losses
Pneumonia as slowly progressive, chronic disease (usually *M. ovipneumoniae)* with soft cough and ocular and nasal discharge. Necropsy: cranioventral lung distribution with sharply demarcated, red-to-greyish areas of consolidation. **Contagious caprine pleuropneumonia** (CCP) with very high morbidity and mortality (*M. capricolum* subsp. *capripneumonie*). Disease complex **Contagious agalactiae** (CA) in sheep and goats with mastitis, arthritis, keratoconjunctivitis, pneumoniae and septicaemia (usually *M. agalactiae,* but also *M. mycoides* subsp. *capri*, *M. capricolum* subsp. *capricolum* and *M. putrefaciens*).

Additional Information/Literature
Iqbal Yatoo M, Raffiq Parray O, Tauseef Bashir S, et al. (2019). Contagious caprine pleuropneumonia - a comprehensive review. Vet Q 39(1):1-25.
DOI 10.1080/01652176.2019.1580826

Jaÿ M, Tardy F. (2019). Contagious Agalactia In Sheep and Goats: Current Perspectives. Vet Med (Auckl). 10:229-247. Published 2019 Dec 27.
DOI 10.2147/VMRR.S201847

Thomas E. Besser, E. Frances Cassirer, Kathleen A. Potter, John VanderSchalie, Allison Fischer, Donald P. Knowles, David R. Herndon, Fred R. Rurangirwa, Glen C. Weiser, Subramaniam Srikumaran (2008). Association of *Mycoplasma ovipneumoniae* Infection with Population-Limiting Respiratory Disease in Free-Ranging Rocky Mountain Bighorn Sheep (*Ovis canadensis canadensis*). J Clin Microbiol 46(2):423-30.

2.2.4.13 Autogenous vaccines against Corynebacterium pseudotuberculosis - infection in small ruminants

Disease/Indication
Caseous Lymphadenitis

Pathogen/Antigen(s)
Corynebacterium pseudotuberculosis: nitrate negative biotype (sheep and goat) and nitrate positive biotype (horse)

Frequency/Importance
The disease caused by *C. pseudotuberculosis* can become endemic in a herd or flock.

Clinical picture and Losses
Pyogranulomas: Starting with abnormal swelling (a “lump”) located in the affected lymph node. Possible fistulation with greenish pus of the necrotic abscess centre. In goats, abscesses are frequently located to the cephalic lymph nodes. Symptoms are often less obvious in pyogranulomas localized in deep tissues or lymph nodes.

Additional Information/Literature
PEPIN, Michel & Paton, Michael (2010). Caseous lymphadenitis in sheep and goats. In P.C. Lefevre, J. Blancou, R. Chermette, G. Uilenberg (Ed.). Infectious and Parasitic Diseases of Livestock (pp.1151-1163).

Dercksen DP, Brinkhof JM, Dekker-Nooren T, et al. A comparison of four serological tests for the diagnosis of caseous lymphadenitis in sheep and goats. Vet Microbiol. 2000;75(2):167-175.

Windsor PA. Control of caseous lymphadenitis. Vet Clin North Am Food Anim Pract. 2011;27(1):193-202.

Williamson LH. Caseous lymphadenitis in small ruminants. Vet Clin North Am Food Anim Pract. 2001;17(2):359-vii.

2.2.4.14 Autogenous vaccines against Erysipelothrix rhusiopathiae - infections in sheep and goats

Disease/Indication
Erysipelas and polyarthritis in sheep and goats

Pathogen/Antigen(s)
Erysipelothrix rhusiopathiae

Frequency/Importance
Infections with *Erysipelothrix rhusiopathiae* can occur frequently in sheep, however they are also rarely reported in goats. Outbreaks are associated with high morbidity and low mortality. The bacterium is widespread in vertebrates and can act as a commensal but also as a pathogen. The main sources of infection are infected or carrier animals, that excrete the bacteria through faeces, urine, saliva and nasal secretions. Additionally, the bacterium can survive in the environment for several weeks.

Clinical picture and Losses
The main clinical picture of *Erysipelothrix rhusiopathiae* infections in small ruminants is a severe polyarthritis in 2- to 6-month-old lambs, that can lead to chronical changes in the joints. Other reports document cases of cutaneous infection, endocarditis, pneumonia and septicaemia.

The reduced growth rate that is commonly related to the clinical symptoms as well as condemnations at the slaughterhouse can have a distinct economic impact on affected small ruminant farms.

Additional Information/Literature
Ersdal et al. (2015). Acute and Chronic *Erysipelothrix rhusiopathiae* Infection in Lambs. Veterinary Pathology, 52(4), 635-643

Palm et al. (2022). An unusual outbreak of erysipelas on a goat farm in Pennsylvania. Journal of Veterinary Diagnostic Investigation, 34:2

Schoiswohl et al. (2020). Polyarthritis caused by *Erysipelothrix rhusiopathiae* in three Austrian sheep flocks- diagnosis, treatment and management measures. Schweizer Archiv für Tierheilkunde, 162(12), 771-780

2.2.4.15 Autogenous vaccines against infectious keratoconjunctivitis in small ruminants

Disease/Indication
Infectious keratoconjunctivitis (IK), pinkeye disease

Pathogen/Antigen(s)
Mycoplasma conjunctivae
Moraxella ovis
Moraxella bovoculi
Listeria monocytogenes
Chlamydia sp.

Frequency/Importance
Infectious keratoconjunctivitis (IK), commonly known as pinkeye disease, is a highly contagious disease affecting small ruminants worldwide. The disease can spread rapidly within a herd through direct contact, nasal or ocular discharges and via insect vectors. Considerable economic impact has been attributed to IK due to reduced productivity and higher costs for antibiotic treatments. *Mycoplasma conjunctivae* is thought be to be major primary pathogen of IK, however *Moraxella sp.* could be isolated more frequently from clinical cases of IK in sheep and goats during recent years.

Clinical picture and Losses
IK can produce ocular discharge, epiphora, mild conjunctivitis and corneal opacity, resulting in transitory blindness in most cases. However, IK outbreaks may result in more severe clinical signs, including infection of the cornea that may lead to ulceration and perforation of the eye which is very painful.

Additional Information/Literature
Williams HJ, Duncan JS, Fisher SN, Coates A, Stokes JE, Gillespie A: Ovine infectious keratoconjunctivitis in sheep: the farmer's perspective. Vet Rec Open. 2019; 6(1):e000321.

Åkerstedt J, Hofshagen M. Bacteriological investigation of infectious keratoconjunctivitis in Norwegian sheep. Acta Vet Scand 2004; 45:19-26.

2.2.5 Autogenous Vaccines for Fish

2.2.5.1 Autogenous vaccines against Francisella orientalis subsp nov. in Tilapia (Oreochromis niloticus)

Disease/Indication
Francisellosis in tilapia

Pathogen/Antigen
Francisella orientalis subsp nov. is a Gram-negative, pleomorphic, facultative intracellular bacterial pathogen affecting tilapia. The pathogen has very recently been reclassified from *Francisella noatunensis* subsp *orientalis* using a genomic approach.

Frequency/importance
Francisella orientalis in tilapia has been reported in wide range of countries including Taiwan, Indonesia, Thailand, Brazil, Costa Rica, USA, UK.

The frequency and importance of *Francisella orientalis* in tilapia is temperature dependent. It is a “winter” disease with outbreaks happening with water temperature below 27 °C. Its impact may reach up to 50% mortality. It is a disease of juvenile fish: affected fish size usually ranges between 0 and 80g with most mortality occurring below 50g.

Clinical pictures and losses
The major external clinical signs are erratic swimming, skin ulcers (primarily at the base of the fins), and gill pallor. At necropsy, the principal pathological features are nephromegaly, splenomegaly, and hepatomegaly, all of which are accompanied by multifocal white nodules. Infections may induce up to 50% mortality. It is a disease of juvenile fish: affected fish size usually ranges between 0 and 80g with most mortality occurring below 50g.

Additional Information/Literature
Chen S.C., Tung M.C., Chen S.P., Tsai J.F., Wang P.C., Chen R.S., Lin S.C. & Adams A. (1994). Systematic granulomas caused by a rickettsia-like organism in Nile tilapia, *Oreochronuis niloticus* (L.), from southern Taiwan. Journal of Fish Diseases 17, 591-599.

Jeffery KR, Stone D, Feist SW, Verner-Jeffreys DW (2010). An outbreak of disease caused by *Francisella* sp. in Nile tilapia *Oreochromis niloticus* at a recirculation fish farm in the UK. Dis Aquat Org 91:161-165. DOI 0.3354/dao02260

Leal CA, Tavares GC, Figueiredo HC (2014). Outbreaks and genetic diversity of *Francisella noatunensis* subsp. *orientalis* isolated from farm-raised Nile tilapia (*Oreochromis niloticus)* in Brazil. Genetics and Molecular Research: GMR 13(3):5704-5712. DOI 10.4238/2014.july.25.26.

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Nguyen, V.V., Dong, H.T., Senapin, S., Pirarat, N. and Rodkhum, C. (2016). *Francisella noatunensis* subsp. *orientalis*, an emerging bacterial pathogen affecting cultured red tilapia (*Oreochromis* sp.) in Thailand. Aquac Res, 47: 3697-3702. DOI 10.1111/are.12802

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2.2.5.2 Autogenous vaccines against Lactococcus garvieae in fish

Disease/Indication
Lactococcosis in fish

Pathogen/Antigen
Lactococcus garvieae are Gram positive cocci included within the family of *Streptococcaceae*. Two serotypes exist, KG+ and KG-. In Tilapia, two serotypes exist. The two serotypes do not cross protect in vaccination and cross protection trials.

Frequency/importance
Lactococcus garvieae is responsible for outbreaks in a large variety of aquatic organisms including but not limited to rainbow trout (*Oncorhynchus mykiss*), Japanese yellowtail (*Seriola quinqueradiata*), tilapia (*Oreochromis spp.*), Japanese eel (*Anguilla japonica*), olive flounder (*Paralichthys olivaceous*) and grey mullet (*Mugil Cephalus*).

Hence, it has a worldwide presence in aquatic organisms of both freshwater and marine waters above 18 °C.
In addition, *L. garvieae* has been isolated from humans in several cases, suggesting that it could be classified as a potential zoonotic agent.

Clinical pictures and losses
Lactococcosis is an hyperacute and haemorrhagic septicaemia causing serious economic losses due to an elevated rate of mortality (up to 50%) and decreased growth rates. Typical external signs are exophthalmia (uni-bilateral), the presence of petechial haemorrhages and a swollen abdomen. *Lactococcus garvieae* can cause outbreaks in all sizes of fish.

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2.2.5.3 Autogenous vaccines against Streptococcus agalactiae in tilapia

Disease/Indication
Streptococcosis in tilapia

Pathogen/Antigen
Streptococci are Gram positive cocci included within the family of *Streptococcaceae*. The main serotypes of *Streptococcus agalactiae* causing severe losses in tilapia are serotypes Ia, Ib and III

Frequency/importance
Streptococcosis is the major bacterial disease of tilapia. Historically, the serotypes were distributed in separated geographical regions. Nevertheless, with transboundary exchanges over the recent years, it is now possible to find more than one serotype of Streptococcus in a given production area. In Latin America and Asia, 3 serotypes of *Streptococcus agalactiae* can be found. In Africa, Sa Ib and Ia are present to date.

Clinical pictures and losses
Streptococcus induce systemic infection in tilapia. Typical external signs are exophthalmia (uni-bilateral), the presence of abscesses on the inferior jaw or at the base of fins, skin haemorrhage and a swollen abdomen. Internal signs include splenomegaly, hepatomegaly and septicaemia. Peritonitis is common. Often, this infection is accompanied by secondary infections due to opportunistic bacteria such as *Aeromonas spp.* and *Vibrio spp*.

Losses happen during the entire life cycle of the fish and can cause up to 30-40% mortality in large fish at the end of the production cycle.

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2.2.5.4 Tilapia Lake Virus (TiLV) in Tilapia (Oreochromis niloticus)

Disease/Indication

Tilapia Lake Virus (TiLV) in tilapia

Pathogen/Antigen

TiLV has been described as an enveloped, negative-sense, single-stranded RNA virus. It has a diameter between 55 and 100 nm.

TiLV has a weak sequence homology to the influenza C virus. The conserved complementary sequences at the 5' and 3' termini are consistent with the genome organization found in orthomyxoviruses.

Frequency/importance

According to scientific publications, TiLV has been identified from samples collected in Israel, Egypt, Ecuador, Colombia and Thailand. It has also been reported in Indonesia, and in Lake Victoria in Africa.

Clinical pictures and losses

Reported clinical signs include lethargy, ocular alterations, skin erosions and discoloration (darkening) and exophthalmia, discoloration (darkening), abdominal distension, scale protrusion and gill pallor. Loss of appetite, abnormal behaviour (e.g. swimming at the surface), and anaemia have also been reported.

Mortality levels of 30-80% have been observed in affected farmed populations. However, the disease has only been reported in a few cases worldwide.

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2.2.5.5 Autogenous vaccines against ISKNV in Tilapia (Oreochromis niloticus)

Disease/Indication
ISKNV in tilapia

Pathogen/Antigen
ISKNV (Infectious Spleen and Kidney Necrosis Virus) is a DNA virus member of the genus *Megalocytivirus* belonging to the iridovirus family.

Frequency/importance
ISKNV in tilapia has been reported in USA, Thailand, Indonesia, Ghana, Mexico, Brazil. It is a potentially devastating disease that spreads through uncontrolled international shipment of live fish.

Clinical pictures and losses
The major external clinical signs are lethargy, gill pallor and abdominal distention. At necropsy, hepatomegaly, splenomegaly, haemorrhagic viscera, friable muscles and presence of ascites are observed. The losses associated with the virus can reach up to 90% mortality in fish of 0.5g to 50g. Mortality in larger fish occur especially when an area is newly affected by the virus. Once the virus is endemic, the outbreaks mainly affect juvenile up to 50-80g.

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2.2.5.6 Autogenous vaccines against Aeromonas veronii in fish

Disease/Indication
Aeromoniasis in fish

Pathogen/Antigen
Aeromonas veronii bv *sobria* is a Gram-negative bacterium with worldwide distribution affecting both freshwater and marine fish species. The pathogen is gaining increasing attention since it may lead to significant losses in aquaculture. The past decade this pathogen has become a serious threat for the Greek and Turkish seabass (*Dicentrarchus labrax*) aquaculture.

Frequency/importance
Disease outbreaks caused by *A. veronii* bv *sobria* accompanied by significant losses have been reported in loach (*Misgurnus anguillicaudatus*) farmed in China (Zhu et al., 2016) and in African catfish (*Clarias gariepinus*), Rajputi (*Puntius gonionotus*), Rui (*Labeo rohita*), Catla (*Catla catla*), and striped snakehead *(Channa striata*) farmed in Bangladesh (Rahman *et al*., 2002). Furthermore, *A. veronii* bv. *sobria* has also been reported to cause disease in ornamental fishes (Sreedharan *et al*., 2013).

Clinical pictures and losses
This pathogen has become extremely problematic during the past few years for the culture of European seabass in Greece. The disease in farmed seabass has been described (Smyrli et al., 2017) and the pathogens have been in-depth characterized using microbiological and genomic methods (Smyrli et al., 2019). The disease outbreaks occur during the warm months of the year when water temperature is over 21^{o}C. Affected fish are usually lethargic with no appetite and in progressed stages of the disease, they have an icteric appearance due to the highly haemolytic nature of the pathogen as well as extensive liver damage. Internally, multiple abscesses are usually found in the spleen, liver and kidney of affected fish.

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2.2.5.7 Autogenous vaccines against Vibrio harveyi in fish

Disease/Indication
Vibriosis in fish

Pathogen/Antigen
Vibrio harveyi is a member of the genus *Vibrio* which contains some of the most important bacterial pathogens of fish and aquatic animals (Austin & Zhang, 2006). *Vibrio harveyi* is the main member of the so-called Harveyi clade of vibrios. It is a pathogen with a wide strain variability (Pujalte et al., 2003). Accurate identification requires the use of advanced molecular tools (Pang et al., 2006).

Frequency/importance
Vibrio harveyi is an opportunistic pathogen usually requiring other stressors to become problematic. The pathogen affects many different hosts in marine waters especially when temperature is above 20°C. Disease outbreaks caused by *Vibrio harveyi* are persistent and very often connected with great losses in the marine aquaculture. Despite that most isolates are susceptible to antibiotics in in vitro testing, treatment of the fish in sea cages is extremely hard and infections are frequently recurrent.

Clinical pictures and losses
The disease is characterized by superficial dermal lesions that may become ulcerative, haemorrhages, ocular lesions and gastroenteritis. In European seabass, cumulative mortalities may reach 50% especially in juvenile fish. The most critical period is following the transfer of the fish from the hatchery to the open sea especially if this concurs with the warmer months of the year.

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2.2.5.8 Autogenous vaccine against Vibrio spp. in Atlantic cod

Disease/indication
Juvenile Vibriosis in Atlantic Cod (*Gadus morhua*). Main clinical signs are erosion and haemorrhages around fins, mouth, and eyes. Congestion of pectoral fins, ascites, fluid-filled intestines, exophthalmia in smaller fish. Systemic infection where bacteria can be isolated from blood and kidney.

Pathogen/Antigen/Serovar/Strain
Vibrio anguillarum subgroups O2a and O2b.

Frequency and significance of disease
Vibriosis, caused by several serotypes of *Vibrio anguillarum*, is a significant bacterial disease of farmed cod in Norway. Bacteria is also found in environment as free-living and can therefore be transmitted over great distances.

Clinical pictures, morbidity, mortality, losses
Lethargic, sluggish, dark-coloured fish observed at the edge of pens near the water surface. Can cause up to 50% mortality in juveniles, lower in larger fish.

Additional Information/Literature
O.B. Samuelsen, A.H. Nerland, T. Jørgensen, M.B. Schrøder, T. Svåsand, Ø. Bergh, Viral and bacterial diseases of Atlantic cod Gadus morhua, their prophylaxis and treatment: a review, Diseases of Aquatic organisms 2006; 71:239-254.

S. Gudmundsdóttir, B. Magnadóttir, B. Björnsdóttir, H. Árnadóttir, B.K. Gudmundsdóttir. Specific and natural antibody response of cod juveniles vaccinated against *Vibrio anguillarum*, Fish & Shellfish Immunology 2009; 26(4):619-624.

Espelid, S., O. M. Rødseth, and T. Ø. Jørgensen. Vaccination experiments and studies of the humoral immune responses in cod, Gadus morhua L., to four strains of monoclonal-defined *Vibrio anguillarum*. Journal of Fish Diseases 14.2 (1991): 185-197.

2.2.5.9 Autogenous vaccine against Pasteurella sp. in Atlantic salmon

Disease/indication
Pasteurellosis in Atlantic salmon. Exophthalmos, peritonitis, pleuritis, pericarditis, petechial bleeding found on organs, peritoneum, swim bladder, septicaemia, discolouring of skin. Pus-filled abscesses in skeletal musculature and on basis of pectoral fins.

Pathogen/Antigen/Serovar/Strain
Pasteurella skyenis
Pasteurella atlantica genomovar salmonicida

Frequency and significance of disease
First described in Norway in 1989 and has caused intermittent outbreaks of disease. Has become a significant disease in the southern parts of Norway since 2018. The disease affects large fish (>3 kg) in seawater at the end of the production cycle. Seen all year around in Western Norway with water temperatures ranging from 8-18 °C.

Clinical pictures, morbidity, mortality, losses
The severity of disease differs, morbidity and mortality are dependent on predisposing factors. Outbreak is often seen about 2 weeks after salmon has been subjected to de-lousing treatment.

Sluggish, lethargic swimming in random patterns and unresponsive to external stimuli. Diseased fish have sign of septicaemia and circulatory failure.

Additional Information/Literature
Sandlund, Nina, et al. *Pasteurella* spp. Infections in Atlantic salmon and lumpsucker. Journal of Fish Diseases 44.8 (2021): 1201-1214.

Strøm, Sverri Biskopstø, and Hanne Nilsen. *Pasteurella skyensis* in Atlantic salmon (Salmo salar L.) in Western Norway. Bulletin of the European Association of Fish Pathologists (2021): 160-168.

Gulla, S., H. Nilsen, A.B. Olsen, and D. Colquhoun. 2020. Fiskepatogene *Pasteurella* I Norge. Norsk Fiskeoppdrett 11: 46–47.

Legård, B.K., and S.B. Strøm. 2020. Pasteurellosis in Atlantic Salmon (Salmo Salar) in Western Norway. Bulletin of the European Association of Fish Pathologists 40 (4): 148-55.

2.2.5.10 Autogenous vaccine against Moritella viscosa in Atlantic salmon

Disease/indication
Causes winter ulcer disease. Extensive ulceration on flanks, gill pallor, fin rot, severe internal pathology.

Pathogen/Antigen/Serovar/Strain
Moritella viscosa, bacterium belonging to *Gammaproteobacteria*

Frequency and significance of disease
Affects several cold-water species, but primarily affects salmonids in sea water. Outbreaks occur across the North Atlantic region when sea water temperature drops below 8-10 °C. Significant welfare problem since fish with extensive ulceration can survive for long periods.

Clinical pictures, morbidity, mortality, losses
Winter ulcer disease starts with superficial ulcers that progresses to chronic skin and muscle ulcers. This may be followed by terminal septicaemia and mortality.
Moribund fish has large pathognomonic ulcers on the flanks, also called “saddle wounds”. Mortality is usually low, less than 10% during outbreak, but causes economical losses due to downgrading of the fillet quality.

Additional Information/Literature
Lunder T, Evensen Ø, Holstad G, Håstein T. “Winter ulcer” in the Atlantic salmon Salmo salar. Pathological and bacteriological investigations and transmission experiments. Diseases of Aquatic Organisms 1995;23:39–49

Colquhoun D, Hovland H, Hellberg H, Haug T, Nilsen H. *Moritella viscosa* isolated from farmed Atlantic cod (Gadus morhua). Bulletin of the European Association of Fish Pathologists 2003;24:109–14

Coyne R, Bergh Ø, Samuelsen O, Andersen K, Lunestad BT, Nilsen H, et al. Attempt to validate breakpoint MIC values estimated from pharmacokinetic data obtained during oxolinic acid therapy of winter ulcer disease in Atlantic salmon (Salmo salar). Aquaculture 2004;238:51–66.

Coyne R, Smith P, Dalsgaard I, Nilsen H, H Kongshaug, Bergh ø, et al. Winter ulcer disease of post-smolt Atlantic salmon: an unsuitable case for treatment? Aquaculture 2006;253:171–8

Benediktsdottir, E., Helgason, S., & Sigurjonsdottir, H. (1998). *Vibrio* spp. isolated from salmonids with shallow skin lesions and reared at low temperature. Journal of Fish Diseases,21(1), 19–28.

2.2.6 Autogenous Vaccines for Dogs and Cats

2.2.6.1 Autogenous vaccines against Pseudomonas - infection in dogs and cats

Disease/Indication
Infections in dogs and cats caused by *Pseudomonas* spp.

Pathogens
Fam. *Pseudomonadaceae*/ Genus *Pseudomonas*/ Species *Pseudomonas*
Pseudomonas aeruginosa is of primary importance. Pseudomonas spp. inhabit the gut of humans and animals. In the environment, especially humid environments, they may remain viable and fecund for a very long time. In the case of *Pseudomonas aeruginosa*, a variety of virulence-associated cell-bound and extracellular factors have been described (endotoxin, extracellular toxins and enzymes). The high resistance of *Pseudomonas aeruginosa* to environmental influences and disinfection procedures favours hospitalism. The low sensitivity to antibiotics can lead to clinical and therapeutic problems. The host spectrum includes all domestic animal species, many zoo and wild animals.

Frequency/Importance
Clinically manifest infections usually require an imbalance of the immune system. In addition to local diseases of the eyes, ears, skin, reproductive organs, mammary gland, lungs and endocard, general septicaemic infections are also described. Resistance to many anti-infectives and disinfectants makes therapy more difficult.

Clinical picture
Pseudomonas aeruginosa is frequently involved in persistent otitis externa in dogs. Predisposed are dogs with long and drooping ears. It usually manifests itself as otitis externa proliferans et ulcerosa. Otitis media can occur as a complication.
In dogs and cats *Pseudomonas aeruginosa* is sometimes detected in connection with infections of the upper respiratory tract and genital tract.

Additional Information/Literature
Selbitz H-J, Truyen U, Valentin-Weigand P (2015). Tiermedizinische Mikrobiologie, Infektions- und Seuchenlehre. 10. ed. Enke, Stuttgart.

2.2.6.2 Autogenous vaccines against Staphylococcus - infection in dogs and cats

Disease/Indication
Infections in dogs and cats caused by *Staphylococcus* spp.; Pyodermia

Pathogens
Genus *Staphylococcus* / 62 species / 30 subspecies, most *S. intermedius* / *pseudintermedius* / *aureus*
For *Staphylococcus* spp. a variety of virulence-associated cell-bound (e.g. capsule, protein A, fibronectin-binding protein) and extracellular factors (e.g. haemolysins, enterotoxins, leucocidin, lipases, hyaluronidase) have been described.

Frequency/Importance
Staphylococcus spp. (most Coagulase-positive) are the cause of various pathological processes in dogs and cats e.g. abscesses, pyodermia, dermatitis, furunculosis, otitis externa, sepsis in whelps, mastitis, pyometra, arthritis, osteomyelitis, pyogenous lesions of organs and wound infections.

S. intermedius plays a special role in this. These diseases are most apparently connected with conditional (e.g. genetic and hormonal) factors.

Clinical picture
Staphylococcus spp. are ubiquitously distributed and also frequently colonize skin and mucous membranes. Clinical symptoms are not always triggered. If the bacteria enter the tissue, they cause purulent changes. These cause different disease patterns in the various organs with corresponding pathological-anatomical and histological changes. The degree of inflammation depends on the resistance of the host organism and especially on the pathogenicity factors of *Staphylococcus spp*.

Additional Information/Literature
Curtis, C.F.; Lamport, A. J.; Lloyd, D. H. (2006). Masked controlled study to investigate the efficacy of a *Staphylococcus intermedius* autogenous bacterin for the control of canine idiopathic superficial pyoderma. Vet. Dermatol. 17: 163-168

Glos, K., Müller, R.S. (2011). Therapie der chronisch rezidivierenden idiopathischen Pyodermie des Hundes mit Staphylokokken-Vakzinen. Tierärztl. Praxis (K) 39: 425-428. DOI 10.1055/s-0038-1623607

Wilson, A., Allers, N., Lloyd, D.H., Bond, R., Loeffler, A. (2019). Reduced antimicrobial prescribing during autogenous staphylococcal bacterin therapy: A retrospective study in dogs with pyoderma. Vet. Rec. 184 (24): 739. DOI 10.1136/vr.105223.

2.2.6.3 Autogenous vaccines against E. coli - infection in dogs and cats

Disease/Indication
Infections in dogs and cats caused by *E. coli,* Diarrhoea, Septicaemia

Pathogens
Fam. *Enterobacteriaceae*/ Genus *Escherichia*/ Species *Escherichia coli*
For *E. coli* a variety of virulence-associated cell-bound and extracellular factors have been described. No specific virulence characteristics are known for dogs and cats. The isolates mostly show haemolysis.

Frequency/Importance
E. coli usually causes diseases of the gastrointestinal tract, urinary tract infections and septicaemia in dogs and cats.

Clinical picture
E. coli - Infections of the gastrointestinal tract usually present as acute to chronic recurrent diarrhoea and are usually influenced by various factors.
E. coli is also important in urinary tract infections in dogs and cats and in connection with infectious puppy mortality.

Additional Information/Literature
Sancak, AA., Rutgers, HC., Hart, CA., Batt, RM (2004). Prevalence of enteropathic *Escherichia coli* in dogs with acute and chronic diarrhoea. Veterinary Record 154, 101-106

Selbitz H-J, Truyen U, Valentin-Weigand P (2015). Tiermedizinische Mikrobiologie, Infektions- und Seuchenlehre. 10. Ed. Enke, Stuttgart.

2.2.6.4 Autogenous vaccines against Papillomavirus - infection in dogs

Disease/Indication
Infections in dogs caused by Papillomavirus, Papillomatosis

Pathogens
Papillomavirus, any of a subgroup of viruses belonging to the family *Papillomaviridae* that infect birds and mammals, causing warts (papillomas) and other most benign tumours, as well as malignant cancers of the genital tract and the uterine cervix in humans.

They are small polygonal viruses containing circular double-stranded DNA (deoxyribonucleic acid). More than 60 distinct types of human papillomaviruses (HPVs) have been identified by DNA analysis, and there are numerous types of animal papillomaviruses, including bovine papillomavirus (BPV), canine oral papillomavirus (COPV) and cottontail rabbit papillomavirus (CRPV; or Shope papillomavirus). The incubation period is usually 4-8 weeks. Papilloma viruses behave strictly host-specific. Depending on the type of virus a preferred localisation is also evident. For additional information see Bovine Papillomatosis.

Frequency/Importance
In dogs epithelial papillomas occur in puppies especially in the mouth cavity and on the lips.
In older animals they usually appear on the head, inside of the ears, eyelids, paws, penis and vagina.

Clinical picture
Skin warts are the most common sign of infection with papillomavirus. Most papillomas -whether found on the skin or occurring in the mucous membranes of the genital, anal, or oral cavities- are benign.
In horses, preferred locations are the head, lateral thorax, lower abdomen and distal extremities.

In the case of oral papillomaviruses in dogs, warts may appear on the lips and spread to the tongue and the mucosal lining inside the oral cavity. These warts may sometimes become so numerous that they interfere with eating. Puppies with weak immune systems are most susceptible to infection, though warts typically regress upon maturation of immune function.

Additional Information/Literature
See literature Bovine Papillomatosis and Equine Sarcoid.

2.2.7 Autogenous Vaccines for Zoo Animals and Captive Wildlife

2.2.7.1 Autogenous vaccines against Clostridium perfringens - infection in zoo/wild animals

Disease/Indication
Clostridiosis

Pathogen/Antigen(s)
Clostridium perfringens
Five toxinotypes (A, B, C, D, E)
Four major toxins (alpha, beta, epsilon, iota)
>15 toxins such as perfringolysin O (*pfo*), enterotoxin (*cpe*), beta2 toxin (*cpb*2)

Clinical picture and Losses
C. perfringens type A: (1) necrotic enteritis (NE) with elevated mortality in several **wild avian species** (such as swan, capercaillies, white storks) including mucosal necrosis restricted to the small intestine with hepatitis, cholangiohepatitis. (2) Haemorrhagic enterocolitis (neither with *cpe* nor *cpb*2 genes) associated with depression, anorexia and bloody diarrhoea, which quickly let to death of **wild carnivore** (Siberian tiger, Amur tiger and a lion). (3) Necrotic and haemorrhagic enteritis in Asiatic black **bears** and **pygmy hogs** (ß2-Toxin; *cpb*2). *Cl. perfringens* type C: (1) lethargy and inappetence followed by sudden death within 24 h post infection in young captive collared and white-lipped **peccaries.**

Additional Information/Literature
Silva RO, Lobato FC (2015). *Clostridium perfringens*: A review of enteric diseases in dogs, cats and wild animals. Anaerobe 33:14-17.
DOI 10.1016/j.anaerobe.2015.01.006

Y. Zhang, Z. Hou, J. Ma (2012). Hemorrhagic enterocolitis and death in two felines (*Panthera tigris altaica* and *Panthera leo*) associated with *Clostridium perfringens* type A, J. Zoo. Wildl. Med. 43: 394e396.

G. Greco, A. Madio, V. Martella, M. Campolo, M. Corrente, D. Buonavoglia, C. Buonavoglia (2005). Enterotoxemia associated with beta2 toxin-producing *Clostridium perfringens* type A in two Asiatic black bears (*Selenarctos thibetanus*), J. Vet. Diag. Invest. 17: 186e189.

B.R. Shome, R. Shome, K.M. Bujarbaruah, A. Das, H. Rahman, G.D. Sharma, B.K. Dutta (2010). Investigation of haemorrhagic enteritis in pygmy hogs (*Sus salvanius*) from India, Rev. Sci. Techno. 29: 687e693.

See also: 2.2.11 Camels and 2.2.13 Psittacines

2.2.8 Autogenous Vaccines for Horses

2.2.8.1 Autogenous vaccines against Streptococcus - infection in horses

Disease/Indication
Infections in horses caused by *Streptococcus* spp.

Pathogens
Fam. *Streptococcaceae*/ Genus *Streptococcus*/ Species *Streptococcus equi*
Streptococci primarily colonize skin and mucous membranes. A number of species are pathogenic to animals with significant differences in hosts and organ systems. For *Streptococcus* spp. a variety of virulence-associated cell-bound and extracellular factors have been described (hyaluronic acid capsule, streptokinase, streptolysin S, leucozidine, mitogenic exotoxins, surface proteins).
Important for the horse are mainly infections with *Streptococcus equi* ssp. *equi* (Strangles) and *Streptococcus equi* subsp. *zooepidemicus*.

Frequency/Importance/Clinical picture
Streptococcus *equi* subsp. *equi* occurs almost exclusively in horses and causes Strangles. A feverish inflammation of the upper respiratory tract with swelling and abscessing of the lymph nodes. Streptococcus *equi* subsp. *zooepidemicus* has a wide range of hosts that includes all domestic animals. It causes respiratory infections, genital infections, umbilical infections and septicaemia in foals.

Additional Information/Literature
Leitlinie zur Impfung von Pferden. 3.ed. 2019. Ständige Impfkommission Veterinärmedizin. Friedrich-Loeffler-Institut, Greifswald. https://www.stiko-vet.fli.de

2.2.8.2 Autogenous vaccines against Papillomavirus - infection in horses

Disease/Indication
Infections in horses caused by Papillomavirus, Equine Sarcoid

Pathogens
Papillomavirus, any of a subgroup of viruses belonging to the family *Papillomaviridae* that infect birds and mammals, causing warts (papillomas) and other most benign tumours, as well as malignant cancers of the genital tract and the uterine cervix in humans.

They are small polygonal viruses containing circular double-stranded DNA (deoxyribonucleic acid). More than 60 distinct types of human papillomaviruses (HPVs) have been identified by DNA analysis, and there are numerous types of animal papillomaviruses, including bovine papillomavirus (BPV), canine oral papillomavirus (COPV) and cottontail rabbit papillomavirus (CRPV; or Shope papillomavirus). The incubation period is usually 4-8 weeks. Papilloma viruses behave strictly host-specific. Depending on the type of virus a preferred localisation is also evident. A special feature is the equine sarcoid in whose genesis bovine papillomaviruses type 1 and 2 play a role. For additional information see Bovine Papillomatosis.

Frequency/Importance
Equine papillomas are extremely rare and usually located on the head (nostrils, mouth, cutaneous mucosa). In contrast, the Sarcoid is a common skin tumour of horses, donkeys and mules.

Clinical picture
Skin warts are the most common sign of infection with papillomavirus. Most papillomas -whether found on the skin or occurring in the mucous membranes of the genital, anal, or oral cavities- are benign.

In horses preferred locations are the head, lateral thorax, lower abdomen and distal extremities.

In the case of oral papillomaviruses in dogs, warts may appear on the lips and spread to the tongue and the mucosal lining inside the oral cavity. These warts may sometimes become so numerous that they interfere with eating. Puppies with weak immune systems are most susceptible to infection, though warts typically regress upon maturation of immune function.

Additional Information/Literature

Rothacker, C. C.; Boyls, A. G.; Levine, D. G. (2015). Autologous vaccination for the treatment of equine sarcoids: 18 cases (2009-2015). Can Vet J 56: 709-714.

Shepard, L. (2016). New Bolton Center research shows equine sarcoid vaccine is effective. University of Pennsylvania (PENN). www.vet.upenn.edu/about/news-room/bellwether/new-bolton-post/new-bolton-post-winter-2016/equine-sarcoid-vaccine.

2.2.9 Autogenous Vaccines for Rabbits

2.2.9.1 Autogenous vaccines against Escherichia coli - infection in rabbits

Disease/Indication
Colibacillosis

Pathogen/Antigen(s)
Rabbit enteropathogenic *Escherichia coli* (REPEC)
Bio-/serogroup: 1+/O109 pathogenic to suckling rabbits, 3-/O15, 4+/O26, 8+/O103 more pathogenic to weaned rabbits, 2+/O128, 2+/O132 less pathogenic to weaned rabbits

Frequency/Importance
Especially newly weaned animals (four to seven weeks-old) are highly vulnerable.

Clinical picture and Losses
Watery yellow diarrhoea with perineal staining, dehydration, and high mortality influenced by stress and diet. At necropsy, caecal content appears totally liquid and sometimes haemorrhagic.

Additional Information/Literature
Peeters JE, Geeroms R, Orskov F. (1988). Biotype, serotype, and pathogenicity of attaching and effacing enteropathogenic *Escherichia coli* strains isolated from diarrheic commercial rabbits. Infect Immun. 56(6):1442-1448.

Boullier S, Milon A (2006). Rabbit colibacillosis. In: Maertens L, Coudert P, (editors): Recent advances in rabbit sciences. Merelbeke: ILVO. 171-179.

Saravia M, Segovia C, Valderrama K, Santander J. (2017). Colibacillosis in a New Zealand white rabbit (*Oryctolagus cuniculus*). J Infect Dev Ctries. 11(2):203-206. Published 2017 Feb 28. DOI 10.3855/jidc.8807.

2.2.9.2 Autogenous vaccines against Pasteurella multocida - infection in rabbits

Disease/Indication
Pasteurellosis

Pathogen/Antigen(s)
Pasteurella multocida, Mannheimia haemolytica

Frequency/Importance
The main source of infection is infectious, chronic carrier rabbits. Natural mating can spread the bacteria from the nasal mucosa of the serving buck to the vaginal mucosa of the doe.

Clinical picture and Losses
The most frequently **respiratory form** shows rhinitis, tracheitis and bronchopneumonia. Typically, hair of nose and forepaws is wet and soiled by nasal discharge. In chronic progression, nasal turbinates can disrupt. Rabbits are sensible for **abscesses** formation caused by *Streptococci*, *Staphylococci* and *Pasteurellaceae*. The **otitis** media supurrativa (OMS) associated with other form of pasteurellosis is particularly asymptomatic. It can develop into otitis interna and/or **encephalitis**. **Metritis** and **vaginitis** caused of *Pasteurella* are known.

Additional Information/Literature
Coudert, P., Rideaud, P., Virag, G., Cerrone, A. (2006). Rabbit colibacillosis. In Maertens L, Coudert P, editors. Recent advances in rabbit sciences. Merelbeke: ILVO. 147-162.

Brown, S. (2012). Abscesses in Rabbits. VeterinaryPartner.com, Small Mammal: Diseases, Small Mammal Health Series.

2.2.9.3 Autogenous vaccines against Bordetella bronchiseptica - infection in rabbits

Disease/Indication
Bordetellosis

Pathogen/Antigen(s)
Bordetella bronchiseptica

Frequency/Importance
B. bronchiseptica infection is often found in association with *Pasteurella multocida*. 4-12 weeks-old rabbits are more likely to develop clinical signs of infection than adults.

Clinical picture and Losses
In rabbits, the pathogenicity of *Bordetella* is uncertain. It may contribute to “snuffles” (rabbit upper respiratory tract infections) and is often found as a co-infection with *P. multocida*.

Additional Information/Literature
Deeb BJ, DiGiacomo RF, Bernard BL, Silbernagel SM. (1990). *Pasteurella multocida* and *Bordetella* bronchiseptica infections in rabbits. Journal of Clinical Microbiology 28(1):70-75.

Glávits R & Magyar T. (1990). The pathology of experimental respiratory infection with *Pasteurella multocida* and *Bordetella bronchiseptica* in rabbits. *Acta Vet Hung.* 38 (3): 211-215.

Zeligs B J, Zeligs J D & Bellanti J A. (1986). Functional and ultrastructural changes in alveolar macrophages from rabbits colonized with *Bordetella bronchiseptica*. *Infect Immun.* 53 (3): 702-706.

2.2.9.4 Autogenous vaccines against Clostridium perfringens - infection in rabbits

Disease/Indication
Epizootic rabbit enteropathy (ERE)

Pathogen/Antigen(s)
Clostridium perfringens Type A (other types are possible) with alpha and additional beta2 toxin

Frequency/Importance
Epizootic rabbit enteropathy is one of main bacterial infections in rabbits.

Clinical picture and Losses
Sharp decrease in feed intake follows abdominal distension and emission of small quantities of watery droppings. The disease frequently leads to death. A caecal impaction associated with mucus in colon and sometimes in small intestine can be observed.

Additional Information/Literature
Marlier D, Dewrée R, Lassence C, et al. (2006). Infectious agents associated with epizootic rabbit enteropathy: isolation and attempts to reproduce the syndrome. Vet J. 172(3):493-500. DOI 10.1016/j.tvjl.2005.07.011

Djukovic, A., Garcia-Garcera, M., Martínez-Paredes, E. et al. (2018). Gut colonization by a novel *Clostridium* species is associated with the onset of epizootic rabbit enteropathy. Vet Res. 123 (49).

2.2.9.5 Autogenous vaccines against Staphylococcus aureus - infection in rabbits

Disease/Indication
Staphylococcosis

Pathogen/Antigen(s)
Staphylococcus aureus

Frequency/Importance
In rabbits, two types of *S. aureus* biotypes can be distinguished. “Low virulence” (LV) isolates are limited to individual animals. “High virulence” (HV) isolates infect a whole flock.

Clinical picture and Losses
Traumatic lesions, umbilical stump in new-born rabbits, the vagina, the preputium or the urethra may be infected by *Staphylococcus aureus* and lead on mastitis, pododermatitis and subcutaneous abscesses.

Additional Information/Literature
Devriese L.A. (1984). A simplified system for biotyping *Staphylococcus aureus*-strains isolated from different animal species. J. Appl. Bact. 215-220.

Holliman A., Girvan G.A. (1986). Staphylococcis in a commercial rabbitry. Vet. Rec., 119, 187-187.

Vancreaynest D., Hermans K., Martel A., Vaneechoutte M., Devriese L.A., Haesebrouck F. (2004). Antimicrobial resistance and resistance genes in *Staphylococcus aureus* strains from rabbits. Vet. Microbio. 101, 245-251.

2.2.10 Autogenous Vaccines for *Mustelidae*

2.2.10.1 Autogenous vaccines against Pseudomonas aeruginosa and Escherichia coli - infection in Mustelidae

Disease/Indication
Haemorrhagic Pneumonia

Pathogen/Antigen(s)
Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Streptococcus equi subsp. *zooepidemicus, Bordetella bronchiseptica*

Frequency/Importance
Animals of all ages, particularly during the (hormone) stress of moult in autumn with mortality range from <1% to 75%. *Escherichia coli* infection as a result of vaccination against *Pseudomonas*.

Clinical picture and Losses
Nasal discharge, dyspnoea, lethargy, anorexia, increased lung sound, cyanosis and fever or sudden death.
In necropsy, gross lesions including haemorrhagic pneumonia with swelling and consolidation of one or more lung lobes.

Additional Information/Literature
Mayer J, Marini RP, Fox JG. (2015). Biology and Diseases of Ferrets. Laboratory Animal Medicine. 577-622.

Salomonsen, C. M. (2012). Haemorrhagic pneumonia in mink caused by *Pseudomonas aeruginosa*. Thesis. Technical University of Denmark.

2.2.10.2 Autogenous vaccines against Arcanobacterium phocae - infection in *Mustelidae*

Disease/Indication
Fur Animal Epidemic Necrotic Pyoderma (FENP)

Pathogen/Antigen(s)
Arcanobacterium phocae

Clinical picture and Losses
Necrotic pyoderma. In mink, paws and facial skin infection; in foxes, infection spreading from eyelids as conjunctivitis to complete facial skin; in raccoon dogs, abscesses in the paws.

Additional Information/Literature
Nonnemann B, Chriél M, Larsen G, Hansen MS, Holm E, Pedersen K. (2017). *Arcanobacterium phocae* infection in mink (*Neovison vison*), seals (*Phoca vitulina*, *Halichoerus grypus*) and otters (*Lutra lutra*). Acta Vet Scand 59(1):74. Published 2017 Oct 26. DOI 10.1186/s13028-017-0342-8

Nordgren H, Aaltonen K, Raunio-Saarnisto M, Sukura A, Vapalahti O, et al. (2016). Experimental Infection of Mink Enforces the Role of *Arcanobacterium phocae* as Causative Agent of Fur Animal Epidemic Necrotic Pyoderma (FENP). PLOS ONE 11(12): e0168129.

2.2.10.3 Autogenous vaccines against Clostridium perfringens - infection in *Mustelidae*

Disease/Indication
Clostridiosis

Pathogen/Antigen(s)
Clostridium perfringens type A

Frequency/Importance
Commonly weanling animals

Clinical picture and Losses
Acute abdominal distension, gastroenteritis, dyspnoea and cyanosis. In necropsy: stomach and intestine filled with gas and brown, semiliquid ingesta.

Additional Information/Literature
Mayer J, Marini RP, Fox JG. (2015). Biology and Diseases of Ferrets. Laboratory Animal Medicine. 577-622.

Macarie I, Cure C, Pop, A, Bittner, S. (1980). Histopathology of natural *Clostridium perfringens* type A infection in mink. Lucrari Stiintifice Institutul Agronomic Nicolae Balcescu 23; 23-27.

Schulman FY, Montali RJ and Hauer PJ. (1993). Gastroenteritis Associated with *Clostridium perfringens* type A in Black-footed ferrets (*Mustela nigripes*). Vet Pathol 308-310.

2.2.10.4 Autogenous vaccines against Campylobacter jejuni -infection in Mustelidae

Disease/Indication
Campylobacteriosis

Pathogen/Antigen(s)
Campylobacter jejuni

Frequency/Importance
Potential for zoonotic transmission from asymptomatic ferrets

Clinical picture and Losses
Self-limiting diarrhoea from mild to watery, anorexia, dehydration, and tenesmus. Septicaemia of pregnant animals characterized by foetal resorption to expulsion of dead or premature living kits

Additional Information/Literature
Bell JA, Manning DD. (1990). Prevalence of *Campylobacter jejuni* in ranch mink at pelting: Cultural, serological, and histological evidence of infection. Can Vet J 31(5):367-371.

Mayer J, Marini RP, Fox JG. (2015). Biology and Diseases of Ferrets. Laboratory Animal Medicine. 577-622.

Hunter, D. B., J. F. Prescott, J. R. Pettit, and, W. E. Show (1983). *Campylobacter jejuni* as a cause of abortion in mink. Can. Vet. J.24:398-399.

Hunter, D. B., J. F. Prescott, D. M. Hoover, G. Hlywka, and J. A. Kerr (1986). Campylobacter colitis in ranch mink in Ontario. Can. J. Vet. Res.50:47-53.

2.2.11 Autogenous Vaccines for Camelidae

2.2.11.1 Autogenous vaccines against Clostridium perfringens type A and C - infection in Camelidae

Disease/Indication
Clostridiosis

Pathogen/Antigen(s)
Five toxinotypes (A, B, C, D, E)
Four major toxins (alpha, beta, epsilon, iota)
>15 toxins such as perfringolysin O (*pfo*), enterotoxin (*cpe*), beta2 toxin (*cpb*2)

Frequency/Importance
Cl. perfringens affects animals in all ages. Training animals appear more infected.

Clinical picture and Losses
Peracute and acute enterotoxaemia (*Cl. perfringens* type A) characterized by sudden death, bloating and constipation, or neurologic signs based on cerebral oedema and/or neuronal necrosis. Calves co-affected with other bacteria show diarrhoea. At necropsy: haemorrhagic loops of bowel and haemorrhagic gastritis, particularly distal portion of the third compartment. **Diarrhoea** is more common in *C. perfringens* type C infection.

Additional Information/Literature
Wernery U, Seifert HS, Billah AM, Ali M. (1991). Predisposing factors in enterotoxemias of camels (*Camelus dromedarius*) caused by *Clostridium perfringens* type A. Rev Elev Med Vet Pays Trop 44(2):147-152.

ANOUSI, S.M.E. and GAMEEL, A. (1993). An Outbreak of Enterotoxaemia in Suckling Camels. Journal of Veterinary Medicine Series A, 40: 525-532.
DOI 10.1111/j.1439-0442.1993.tb00661.x

Thedford TR, Johnson LW. (1989). Infectious diseases of New-World camelids (NWC). Vet Clin North Am Food Anim Pract 5(1):145-157.
DOI 10.1016/s0749-0720(15)31007-0

Fayez, M. (2013). *Clostridium perfringens* Enterotoxaemia in Camel (*Camelus dromedarius*) Calves. Int. J. Curr. Adv. Res.; 1(5):239-247.

2.2.11.2 Autogenous vaccines against Escherichia coli -infection in Camelidae

Disease/Indication
Colibacillosis

Pathogen/Antigen(s)
Escherichia coli, enterotoxic and septicaemic strains

Frequency/Importance
New World Camelid neonates [<7 d]. Older animals with bacterial or viral co-infection.

Clinical picture and Losses
Watery diarrhoea and **sepsis** in neonates associated with a failure of passive transfer of maternal antibodies.

Additional Information/Literature
Bessalah S, Fairbrother JM, Salhi I, et al. (2016). Antimicrobial resistance and molecular characterization of virulence genes, phylogenetic groups of *Escherichia coli* isolated from diarrheic and healthy camel-calves in Tunisia.
Comp Immunol Microbiol Infect Dis 49:1-7. DOI 10.1016/j.cimid.2016.08.008

El-Sayed A, Ahmed S, Awad W. (2008). Do camels (Camelus dromedarius) play an epidemiological role in the spread of Shiga Toxin producing *Escherichia coli (*STEC) infection? Trop Anim Health Prod 40(6):469-473. DOI 10.1007/s11250-007-9122-1

Salehi, T.Z., Tonelli, A., Mazza, A. et al. (2012). Genetic Characterization of O157:H7 Strains Isolated from the One-Humped Camel (Camelus dromedarius) by Using Microarray DNA Technology. Mol Biotechnol 51, 283-288.
DOI 10.1007/s12033-011-9466-7

Whitehead CE. (2009). Neonatal diseases in llamas and alpacas. Vet Clin North Am Food Anim Pract 25(2):367-384. DOI 10.1016/j.cvfa.2009.03.002.

2.2.11.3 Autogenous vaccines against Streptococcus equi subsp. zooepidemicus - infection in Camelidae

Disease/Indication
Alpaca fever

Pathogen/Antigen(s)
Streptococcus equi subsp. *zooepidemicus*

Frequency/Importance
Acute forms in young animals. **Chronic** forms more common in adults. Regional differences in clinic symptoms in *Camelidae*.

Clinical picture and Losses
Septicaemia characterized by elevated temperature, depression, digestive tract alterations, recumbency and death (**acute** form). In necropsy: **polyserositis**. The **chronic** forms with **multiple abscesses** and orchitis; eventually death in 4-8 days after first symptoms.

Additional Information/Literature
Corpa JM, Carvallo F, Anderson ML, Nyaoke AC, Moore JD, Uzal FA (2018). *Streptococcus equi* subspecies *zooepidemicus* septicemia in alpacas: three cases and review of the literature. J Vet Diagn Invest 30(4):598-602.
DOI 10.1177/1040638718772071

Fowler ME, Bravo PW (2010). Infectious diseases. In: Fowler ME, Bravo PW, eds. Medicine and Surgery of Camelids. 3rd ed. Ames, IA: Blackwell.173–230.

Jones M, et al. (2009). Outbreak of *Streptococcus equi* ssp. *zooepidemicus* polyserositis in an alpaca herd. J Vet Intern Med 23:220-223.

Stoughton WB, Gold J (2015). *Streptococcus equi* subsp *zooepidemicus* pleuropneumonia and peritonitis in a dromedary camel (Camelus dromedarius) calf in North America. J Am Vet Med Assoc 247:300–303.

2.2.11.4 Autogenous vaccines against Caseous Lymphadenitis in camelids

Disease/Indication
Caseous Lymphadenitis (CLA), Pseudotuberculosis

Pathogen/Antigen(s)
Corynebacterium pseudotuberculosis

Frequency/Importance
Caseous Lymphadenitis (CLA) is one of the most important bacterial infections in livestock and can affect sheep, goat, cattle, camelids, and equids. It is caused by *Corynebacterium pseudotuberculosis* and is characterized by abscessation of one or more superficial lymph nodes and sometimes causes infection of internal organs including mammary gland. The infection is spread by inhalation, ingestion or directly through wounds. CLA has been reported in Old World Camels from all camel rearing countries worldwide including Europe as well as in South American Camelids. The virulence of the pathogen is attributed to its exotoxin phospholipase D which is produced by all *C. pseudotuberculosis* strains. Two biotypes exist: ovine/caprine (serotype I or biotype ovis) and equine/bovine (serotype II or biotype bovis). Both have been isolated in Old World Camels and South American Camelids.

Clinical picture and Losses
CLA is a chronic contagious disease and the intracellular bacterium forms abscesses in external and internal lymph nodes. These abscesses enlarge, may rupture and discharge infectious pus. The disease can cause severe economic losses. Pathognomonic in camels are cold, closed painless abscesses up to the size of a lemon or orange in the external lymph nodes.

Additional Information/Literature
U Wernery and J Kinne. Caseous Lymphadenitis (Pseudotuberculosis) in Camelids: A Review. Austin J Vet Sci & Anim Husb. 2016; 3(1): 1022.

2.2.12 Autogenous Vaccines for Pigeons

2.2.12.1 Autogenous vaccines against E. coli - infection in pigeons

Disease/Indication
Escherichia coli-infection
Colisepticemia, coligranuloma, air sac disease (chronic respiratory disease, CRD), swollen-head syndrome, venereal colibacillosis, peritonitis, salpingitis, orchitis, osteomyelitis, synovitis, arthritis, omphalitis, panophthalmitis, enteritis and cellulitis of poultry (1, 2, 3, 4)

Pathogen/Antigen(s)
Escherichia coli (most common serotypes: O78 and O2)

Frequency/Importance
Frequently found in pigeons. Antimicrobial resistance strains were also found in pigeons.

Even though no reports of direct transmission of *E. coli* from pigeons to humans yet, there is a possibility of a zoonotic risk.

Clinical picture and Losses
Enteritis, green diarrhoea, vomiting, refusal of feed, increased water uptake, lameness or a dropped wing caused by joint infection, onset of emaciation and sudden death.

It can cause high mortality in an occurrence of secondary infection after herpesviral or adenoviral infection.

Additional Information/Literature
Kumar, Arvind; Tiwary, Bipransh Kumar; Kachhap, Sangita; Nanda, Ashis Kumar; Chakraborty, Ranadhir (2015). An *Escherichia coli* strain, PGB01, isolated from feral pigeon Faeces, thermally fit to survive in pigeon, shows high level resistance to trimethoprim. In PloS one 10 (3), e0119329. DOI 10.1371/journal.pone.0119329.

Radimersky, T.; Frolkova, P.; Janoszowska, D.; Dolejska, M.; Svec, P.; Roubalova, E. et al. (2010). Antibiotic resistance in faecal bacteria (*Escherichia coli*, *Enterococcus* spp.) in feral pigeons. In Journal of applied microbiology 109 (5), pp. 1687–1695. DOI 10.1111/j.1365-2672.2010.04797.x.

Vasconcelos, Ruben Horn; Teixeira, Régis Siqueira de Castro; Silva, Isaac Neto Goes da; Lopes, Elisângela de Souza; Maciel, William Cardoso (2018). Feral pigeons

(Columba livia) as potential reservoirs of *Salmonella* sp. and *Escherichia coli*. In Arq. Inst. Biol. 85 (0). DOI 10.1590/1808-1657000412017.

Wages, Dennis Paul (1987). Diseases of Pigeons. In Veterinary Clinics of North America: Small Animal Practice 17 (5), pp. 1089-1107.
DOI 10.1016/S0195-5616(87)50106-1.

2.2.12.2 Autogenous vaccines against Enterococcus spp. - infection in pigeons

Disease/Indication
Enterococcosis

Pathogen/Antigen(s)
Enterococcus spp.

Frequency/Importance
Frequently found in pigeons. Antibiotic resistance against these bacteria were found in pigeons

Clinical picture and Losses
Acute form: septicaemia and include depression, lethargy, ruffled feathers, diarrhoea, and a decrease in egg production
subacute/chronic form: depression, lameness, head tremors and paralysis due to inflammation in the spinal column, especially at the free thoracic vertebra may be noted. If untreated, most affected birds die

Additional Information/Literature
Radimersky, T.; Frolkova, P.; Janoszowska, D.; Dolejska, M.; Svec, P.; Roubalova, E. et al. (2010). Antibiotic resistance in faecal bacteria (*Escherichia coli, Enterococcus* spp.) in feral pigeons. In Journal of applied microbiology 109 (5), pp. 1687-1695. DOI 10.1111/j.1365-2672.2010.04797.x.

Wages, Dennis Paul (1987). Diseases of Pigeons. In Veterinary Clinics of North America: Small Animal Practice 17 (5), pp. 1089-1107. DOI 10.1016/S0195-5616(87)50106-1.

2.2.12.3 Autogenous vaccines against Salmonella - infection in pigeons

Disease/Indication
Pigeon salmonellosis

Pathogen/Antigen(s)
Host specific, highly virulent
Salmonella Typhimurium var. Copenhagen
Others
Salmonella Typhimuriu*m (other var.)*
Salmonella Enteritidis
Salmonella Agona
Salmonella Montevideo
Salmonella Virginia

Frequency/Importance
Infected pigeon lofts may have mortality in squabs and occasional deaths in adult pigeons

Clinical picture and Losses
Variable levels of severity
Weight loss
Diarrhoea
Polyuria
Lame- ness
Inability to fly.

Additional Information/Literature
Pasmans F. et. al. (2004). Assessment of Virulence of Pigeon Isolates of *Salmonella enterica* subsp. *Enterica* Serovar Typhimurium Variant Copenhagen for Humans.
J Clin Microbiol. 42(5): 2000-2002

Vereecken et. al. (2000). The effect of vaccination on the course of an experimental *Salmonella typhimurium* infection in racing pigeons. Avian Pathology 29, 465-471

Afaf et. al. (2016). Determination of the optimal protective dose of inactivated *Salmonella typhimurium* vaccine in pigeon.
Benha Veterinary Medicine Journal, Vol.31, No 1:73-77

2.2.12.4 Autogenous vaccines against Streptococcus - infection in pigeons

Disease/Indication
Streptococcosis

Pathogen/Antigen(s)
Streptococcus gallolyticus
5 biotypes: determined by their haemolytic properties, polysaccharide production and carbohydrate fermentation
5 serotypes: determined by agglutination
6 supernatant phenotypes determined based on presence/absence of supernatant proteins T1, T2, T3 and A protein
Highly virulent strains: presence of A protein and fimbriae
Moderate to low virulent strains: presence of only T2 or T3

Frequency/Importance
Regarded as facultative pathogen
Mortality related to septicaemia

Clinical picture and Losses
Acute mortality, inability to fly, lameness, weight loss and slimy green diarrhoea
Circumscribed areas of necrosis in the pectoral muscle
Supracoracoid muscle and arthritis of the knee, shoulder and hock

Additional Information/Literature
de Herdt, P.; Pasmans, F. (2009). Handbook of avian medicine. Chapter 15, 350-376

Van Der Toorn F., Lumeij JT. (2001). *Streptococcus gallolyticus* infections in racing pigeons, a literature review. Tijdschr Diergeneeskd. 126(3):66-71

2.2.12.5 Autogenous vaccines against Mycoplasma - infection in pigeons

Disease/Indication
Mycoplasmosis

Pathogen/Antigen(s)
Mycoplasma gallisepticum
M. columbinum
M. columborale
M. columbinasale

Frequency/Importance
Low prevalence
Chronic respiratory disease
Can be vertically transmitted – important eradication in breeder flocks

Clinical picture and Losses
Coughing
Nasal and ocular discharge
Poor productivity
Slow growth
Stunting
Inappetence
Reduced hatchability
Occasional hatchability and abnormal feathers.

Additional Information/Literature
Keymer IF. et. al. (1984). Isolation of *Mycoplasma* spp. from racing pigeons (*Columba livia*). Avian Pathol. 13(1):65-74

2.2.12.6 Autogenous vaccines against Adenovirus - infection in pigeons

Disease/Indication
Type 1 and 2 adenovirosis (classical adenovirosis, necrotizing hepatitis)
Young pigeon disease syndrome (YPDS)

Pathogen/Antigen(s)
Type I adenovirus (PiAd-1) and Type II adenovirus (PiAd-2)

Frequency/Importance
Cause serious harm to the pigeon population (12% of the 2338 pigeon submission during autopsy of pigeons at the Gent Univ.). Infected pigeons are susceptible with secondary infection of *E. coli*.

Clinical picture and Losses
1. Type 1 adenovirosis (Classical adenovirosis)
   A. Clinical signs: vomiting, acute watery diarrhoea and weight losses (catarrhal enteritis)
   B. Infection spread: within 2 days, all pigeons in a loft may be affected
   C. Mortality: 0-20% (w/o secondary bacterial infection)
   D. Adeno/coli syndrome – Both Adenovirus and *E. coli* infected pigeons die rapidly and acutely from *E. coli* septicaemia
2. Type 2 adenovirosis (Necrotizing hepatitis)
   A. Clinical signs: vomiting, production of yellow watery droppings, green and foul diarrhoea, emaciation and severe weakening, eventually resulting in death
   B. Infection spread: some pigeons die acutely (sudden death) while others remain clinically normal
   C. Mortality: 30-70% (may reach 100%)

Additional information/Literature
Herdt, P. de; Ducatelle, R.; Lepoudre, C.; Charlier, G.; Nauwynck, H. (1995). An epidemic of fatal hepatic necrosis of viral origin in racing pigeons (Columba livia). In Avian pathology: journal of the W.V.P.A 24 (3), pp. 475-483. DOI 10.1080/03079459508419087

Marlier, D.; Vindevogel, H. (2006). Viral infections in pigeons. In Veterinary journal (London, England: 1997) 172 (1), pp. 40–51. DOI 10.1016/j.tvjl.2005.02.026

Vereecken, M.; Herdt, P. de; Ducatelle, R. (1998). Adenovirus infections in pigeons: A review. In Avian pathology: journal of the W.V.P.A 27 (4), pp. 333-338. DOI 10.1080/03079459808419348

Wan, Chunhe; Chen, Cuiteng; Cheng, Longfei; Shi, Shaohua; Fu, Guanghua; Liu, Rongchang et al. (2018). Detection of novel adenovirus in sick pigeons. In: The Journal of veterinary medical science 80 (6), pp. 1025–1028. DOI 10.1292/jvms.18-0024

Furthermore, *Fowl Adenoviruses* are infective to pigeons. *FAdV-2, 4, 5, 6, 8, 10* and *12* have been isolated from pigeons. The information about *FAdV* can be found in *Adenovirus*-poultry section

2.2.12.7 Autogenous vaccines against Astrovirus - infection in pigeons

Disease/Indication
Astrovirus infection

Pathogen/Antigen(s)
Avian nephritis virus (*ANV-1* and *-2*), (2 not yet accepted virus strains, *Wood pigeon astrovirus (WPiAstV)* and *Feral pigeon astrovirus (FPiAstV)*)

Frequency/Importance
79.4% of feral pigeons (85/107) and 66.7% wood pigeons (6/9) had Astrovirus infection

Clinical picture and Losses
Enteritis, hepatitis, nephritis, diarrhoea, gastrointestinal illness, urinary tract and renal disease

Additional Information/Literature
Koci, Matthew D.; Schultz-Cherry, Stacey (2002). Avian astroviruses. In Avian pathology: journal of the W.V.P.A 31 (3), pp. 213-227
DOI 10.1080/03079450220136521

Kofstad, Tone; Jonassen, Christine M. (2011). Screening of feral and wood pigeons for viruses harbouring a conserved mobile viral element: characterization of novel Astroviruses and Picornaviruses. In PloS one 6 (10), e25964
DOI 10.1371/journal.pone.0025964

Pantin-Jackwood, Mary; Todd, Daniel; Koci, Matthew D. (2013). Avian Astroviruses. In Stacey Schultz-Cherry (Ed.): Astrovirus Research. New York, NY: Springer New York, pp. 151–180

Zhao, W.; Zhu, A. L.; Yu, Y.; Yuan, C. L.; Zhu, C. X.; Yang, Z. B. et al. (2011a). Complete sequence and genetic characterization of pigeon avian nephritis virus, a member of the family Astroviridae. In Archives of virology 156 (9), pp. 1559-1565.
DOI 10.1007/s00705-011-1034-8

Zhao, W.; Zhu, A. L.; Yuan, C. L.; Yu, Y.; Zhu, C. X.; Lan, D. L. et al. (2011b). Detection of astrovirus infection in pigeons (Columbia livia) during an outbreak of diarrhoea. In Avian pathology: journal of the W.V.P.A 40 (4), pp. 361-365.
DOI 10.1080/03079457.2011.587792

2.2.12.8 Autogenous vaccines against Herpesvirus - infection in pigeons

Disease/Indication
Pigeon Herpesvirus

Pathogen/Antigen(s)
Columbid herpesvirus-1," or CoHV-1 (genotype)

Frequency/Importance
Herpes encephalomyelitis virus: rare
Inclusion body hepatitis: 50% occurrence when introduced in flock, 10-15% mortality
Surviving birds are immune but carriers: breeders will pass the virus on to their offspring

The offspring will not, however, develop disease (passive transfer of immunity)
The virus, becomes therefore enzootic in the flock but clinically inapparent unless an outbreak of disease occurs when animals are immunosuppressed or when the passive transfer of immunity is missing

Clinical picture and Losses
Herpes encephalomyelitis virus: lack of coordination and paralysis.
Inclusion body hepatitis: hepatitis, enteritis, pancreatitis, ingluvitis and stomatitis
Respiratory disease: conjunctivitis, nasal discharge and necrotic foci or ulcerations of the pharynx and larynx

Additional Information/Literature
Marlier et. al. (2006). Viral infections in pigeons. The Veterinary Journal 172: 40-51

2.2.12.9 Autogenous vaccines against Rotavirus - infection in pigeons

Disease/Indication
Pigeon rotavirus infection

Pathogen/Antigen(s)
Rotavirus A
One genotype (G18[P17]) known.

Frequency/Importance
Variable mortality, from none to more than 50%
Associated with young pigeon disease syndrome

Clinical picture and Losses
Apathy
Anorexia
Slimy diarrhoea
Vomiting
Congested crops

Additional Information/Literature
Rubbenstroth D. et. al. (2019). Identification of a novel clade of group A rotaviruses in fatally diseased domestic pigeons in Europe. Transbound Emerg Dis. 66(1):552-561. DOI 10.1111/tbed.13065. Epub 2018 Nov 28

Rubbenstroth D. et. al. (2020). First experimental proof of Rotavirus A (RVA) genotype G18P[17] inducing the clinical presentation of “young pigeon disease syndrome” (YPDS) in domestic pigeons (Columba livia).Transboundary and Emerging Diseases 00:1-10

2.2.13 Autogenous Vaccines for Psittacines/Passerines

2.2.13.1 Autogenous vaccines against Circovirus - infection in psittacines / passerines

Disease/Indication
Psittacine beak and feather disease (PBFD) / Passerine circoviral infection

Pathogen/Antigen(s)
Nine avian virus species, which are *Beak and feather disease virus (BFDV), Goose circovirus, Duck circovirus, Swan circovirus, Gull circovirus, Pigeon circovirus, Canary circovirus, Finch circovirus, and Starling circovirus*

Frequency/Importance
High prevalence

Clinical picture and Losses
PBFD:
High mortality (young and neonatal birds)
Peracute form: Enteritis, pneumonia, weight loss and eventual dead
Beak and feather abnormalities: Lack of powder down on beak, abnormal formation of growing feathers: Pinched feathers, clubbed at the base, haemorrhage in developing shaft, feather pigment loss, Immunosuppression,
Subclinical form

Passerine circovival infection:
Apathy, anorexia, depression, swelling and a reddish colouring of the abdomen, high mortality
nasal discharge, dyspnoea, anorexia, depression and a very high mortality (50%) in both adult and young birds. Gross and histopathology revealed moderate to severe lymphoid depletion in the bursa of Fabricius and thymus, and sinusitis/rhinitis, tracheitis, bronchopneumonia, myocarditis, nephritis and splenitis

Additional Information/Literature
Raidal S.R. et. al. (2015). Review on psittacine beak and feather disease and its effect on Australian endangered species. Vet J 93(12):466-70

2.2.13.2 Autogenous vaccines against Herpesvirus - infection in psittacines

Disease/Indication
Pacheco's disease

Pathogen/Antigen(s)
Psittacid herpesvirus 1 (PsHV-1)
Four genotypes

Frequency/Importance
Common, often fatal

Clinical picture and Losses
Hepatomegaly, splenomegaly, and renomegaly
Mottled liver or grossly discoloured
Pericardial ecchymotic and petechial haemorrhages

Additional Information/Literature
Barao da Cunha M. et. al. (2007). Pacheco's parrot disease in macaws of the Lisbon's Zoological Garden. Description of an outbreak, diagnosis and management, including vaccination. Dtsch Tierarztl Wochenschr. 114(11):423-8

Tomaszewski E. et. al. (2001). Detection and Heterogeneity of Herpesviruses Causing Pacheco's Disease in Parrot. J Clin Microbiol 39(2): 533-538

2.2.13.3 Autogenous vaccines against Polyomavirus - infection in psittacines / passerines

Disease/Indication
Budgerigar fledgling disease, Psittacine polyomavirus, Passerine polyomavirus

Pathogen/Antigen(s)
Avian polyomavirus (Papovavirus)

Frequency/Importance
Peracute to acute death of pre-weaned neonates
Adults typically resistant to infection, high prevalence

Clinical picture and Losses
Acute onset of lethargy, crop stasis, and death within 24-48 hours. Cutaneous haemorrhage, abdominal distention, and feather abnormalities
Surviving budgerigars > 3-week old often exhibit feather dystrophy. In other species of psittacines < 4-month old, the infection is also often fatal.
Kidneys and liver: enlarged, may be pale, congested, mottled, or have pinpoint, white foci. Petechial or ecchymotic haemorrhages may also be present on viscera, particularly the heart. The heart is sometimes enlarged and may show hydropericardium. Intranuclear inclusion bodies are often seen in the liver, kidneys, heart, spleen, bone marrow, uropygial gland, skin, feather follicles, etc.

Additional Information/Literature
Ritchie B.W et al. (1996). An inactivated avian polyomavirus vaccine is safe and immunogenic in various Psittaciformes. Vaccine 14: 1103-1107

Johne R. et al. (1998). Avian polymavirus in wild birds: genome analysis of isolates from Falconiformes and Psittaciformes.
https://www.ncbi.nlm.nih.gov/pubmed/9739329 Arch Virol 143(8):1501-12

2.2.13.4 Autogenous vaccines against Paramyxovirus - infection in psittacines

Disease/Indication
Newcastle disease (Exotic Newcastle Disease)

Pathogen/Antigen(s)
Avian paramyxovirus serotype 1 and 3 = APMV-1, APMV-3
(In total, 9 serotypes recognized: APMV1-9)

Frequency/Importance
Acute lethal infections, usually with haemorrhagic lesions in the intestines of dead birds

Clinical picture and Losses
APMV-1
Depression, anorexia, weight loss, sneezing, nasal discharge, dyspnoea, conjunctivitis, bright yellow-green diarrhoea, ataxia, head bobbing, and opisthotonos
In prolonged cases, unilateral or bilateral wing and leg paralysis, chorea, torticollis, and dilated pupils also may be seen.
Lesions include hepatomegaly, splenomegaly, petechial or ecchymotic haemorrhages on serosal surfaces of all viscera and air sacs, airsacculitis, and excess straw-coloured peritoneal fluid
APMV-3
Acute pancreatitis (Neophema spp.: high mortality), lymphoplasmocytic myocarditis, and central nervous system symptoms (a.o. torticollis)

Additional Information/Literature
Alexander D. J. (2000). Newcastle disease and other avian paramyxoviruses.
Rev. sci. tech. Off. int. Epiz.19 (2), 443-462

2.2.13.5 Autogenous vaccines against Chlamydia psittaci - infection in psittacines

Disease/Indication
Avian chlamydiosis (AC), psittacosis, ornithosis

Pathogen/Antigen(s)
Chlamydia psittaci
Six serotypes known to infect birds (A-F) – A and F are the main serotypes associated with psittacines
Chlamydia avium

Frequency/Importance
Severity depends on virulence, infectious dose, stress factors and susceptibility
Asymptomatic infections are common

Clinical picture and Losses
Cachexia, anorexia
Nasal and ocular discharge, conjunctivitis, sinusitis, dyspnoea
Yellow-green droppings – diarrhoea.

Additional Information/Literature
Andersen A.A. et al. (2000). Avian chlamydiosis. Rev. sci. tech. off. Int. epiz. 19(2),396-404

2.2.13.6 Autogenous vaccines against Aspergillosis - infection in psittacines

Disease/Indication
Aspergillosis

Pathogen/Antigen(s)
Aspergillus fumigatus

Frequency/Importance
All species, ages and sexes can be affected
Major cause of mortality in captive birds

Clinical picture and Losses
Depression, inappetence, reluctance to fly/perch, dropped wings
Weight loss, dyspnoea, tachypnoea, cyanosis
Lethargy, polyuria/polydipsia, tail bobbing, and/or enlarged nares.

Additional Information/Literature
Fischer D, Lierz M (2015). Diagnostic procedures and available techniques for the diagnosis of aspergillosis in birds. J Exotic Pet Med *24*(3):283-295

Krautwald-Junghanns ME, Vorbrüggen S, Böhme J (2015). Aspergillosis in birds: an overview of treatment options and regimens. J Exotic Pet Med 24(3):296-307

Beernaert LA, Pasmans F, Van Waeyenberghe L, Haesebrouck F (2010). *Aspergillus* infections in birds: a review. Avian Pathol 39:325-231

2.2.13.7 Autogenous vaccines against Yersinia spp. - infection in psittacines / passerines

Disease/Indication
Yersiniosis

Pathogen/Antigen(s)
Yersinia pseudotuberculosis

Frequency/Importance
Acute illness and mortality

Clinical picture and Losses
Pneumonia, enteritis with wet diarrhoeic droppings
Acute cases: enlarged, patchily discoloured liver
Chronic cases: miliary white spots throughout the liver, kidneys and spleen.

Additional Information/Literature
Harcourt-Brown, N.; Chitty, J. (2005). BSAV Manual of Psittacine Birds. 2nd ed. British Small Animal Veterinary Association

lly, T. et al. (ed.) (2009). Handbook of Avian Medicine. 2nd ed., Elsevier

3. Specific Keeping, Management and Production Conditions Influencing the Use of Autogenous Vaccines

3.1 Autogenous Vaccines for Poultry

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3.1.1. Importance of prophylactic strategies in poultry production

Commercial poultry production has observed big changes during the recent decades and is now generally characterized by large to very large flock sizes, which in some cases number more than 100,000 animals in the same unit. This has increased the risk and impact of infectious diseases, which upon introduction have the potential of asserting devastating effects during a short course of time. Therefore, rigid disease prevention strategies have become increasingly important, not only to prevent animal suffering, increased mortality and condemnation rates and thereby economic losses, but also to support protection of consumers. The reduction of antibiotic use in poultry has also gained importance and is now an important goal worldwide to reduce the risk of antimicrobially resistant bacteria.

Key preventive strategies include implementation of appropriate hygiene and biosecurity measures; maintenance of gut homeostasis; reduction of stress and enhancement of host immunity. The latter includes genetically and epigenetically based natural disease resistance as well as passive and active immunization.

3.1.2. General aspects of vaccination in poultry

Active and passive immunization in poultry is widely used to reduce the risk and consequences of exposure to pathogens. Live as well as recombinant, subunit and killed vaccines are internationally licensed for use in poultry. Depending on the pathogen, vaccines are intended to protect the individual bird against disease, reduce shedding and subsequent spread of the pathogen. Complete avoidance of transmission through vaccination is rarely achieved under field conditions. Vaccines may also be used to induce immunity in the parent birds to pass maternal antibodies to progeny to prevent early infection when the chick's immune system is still poorly developed. Other vaccination approaches may prevent disease in the breeders and subsequent vertical transmission to the embryo and chick (Collett and Smith, 2020).
The type of vaccine selected to prevent a specific disease depends on the

characteristics of the pathogen and the nature of the pathogen-host interaction.

While antibodies are important for protection against some pathogens *e.g.* Newcastle disease virus, others may mainly require a cell-mediated response *e.g.* Marek's disease virus. For some diseases, stimulation of systemic immunity seems to be most protective while local defence mechanisms may be important for the control of pathogens infecting through mucosal surfaces. Importantly, vaccines or their components should also stimulate innate immune parameters contributing to pathogen control particularly in the very early phase after vaccine application. This may additionally lead to beneficial effects on the control of non-related pathogens (Byrne et al., 2020).

There is a delicate balance between high antigenicity and absence of adverse effects from vaccine formulations. In general, live replicating vaccines, which are only marginally attenuated, typically induce a stronger immune response, yet may, under certain circumstances, lead to adverse vaccine reactions. On the contrary, fully inactivated autogenous vaccines should be free of virulence-associated factors and thereby safe. Inactivation may, however, not ensure freedom from toxic contents like endotoxins, and therefore, autogenous vaccines should be administered first to a small group of birds to confirm harmlessness before a whole flock is immunized (Hera and Bures, 2004).

Modified live vaccines, specifically viral live vaccines, replicate in infected cells and may undergo processing as endogenous antigens to specifically trigger the activity of cytotoxic T cells. Killed organisms act as exogenous antigens and subsequently stimulate a Th2-cell dominated response and antibodies (Tizard, 2004). Inactivated, adjuvanted vaccines may induce high levels of circulating antibodies, while being less able of stimulating local and cell-mediated immunity. Live vaccines may induce a stronger local and cell-mediated immunity while a lower antibody level, which, depending on the vaccine and pathogen type, may stimulate immunity of a shorter duration (Legnardi et al., 2020).

Commercial licensed live vaccines are available to protect poultry against various bacteria, viruses and Eimeria species. Most live vaccines are suitable for mass application. Inactivated vaccines are available against viral and bacterial pathogens, and normally adjuvanted and therefore must be administered by individual injection.

In general, the efficacy of a vaccination depends on the bird species and genotype, age of birds with respect to the maturity of the immune system, pre-existing immunity (interfering maternally derived antibody levels), adjuvants used and the application route.

Vaccines are normally licensed based on experimental and field protection studies. Licensed vaccines are also tested for possible adverse effects. These tests are normally not performed for autogenous vaccines, as their use is intended for immediate protection of birds against current pathogens in epidemiologically related flocks. But the safety of the autogenous vaccines for the animal must also be guaranteed by the vaccine producer.

3.1.3. Poultry disease prevention through vaccination

Vaccination is an important and widely used prophylactic tool for disease prevention in poultry. For most major infectious agents licensed commercial vaccines are available yet depending on the bird species and not least the poultry production system, the number of licensed vaccines in Europe varies.

A variety of different vaccines are licensed for the control of infectious diseases of major health or economic concern. These include for example vaccines against the notifiable Newcastle disease virus, Infectious Bronchitis virus and Infectious Bursal Disease. Vaccines against organism with a limited antigenic diversity have been particularly effective whereas for other organism and particularly most bacterial pathogens common occurrence of antigenically different pathotypes rarely allows efficient disease prevention by licensed vaccines (Ghunaim et al., 2014; Bande et al., 2015; Boudaoud et al., 2016).

While the list of infectious causes in the confined European poultry production is similar to the alternative systems where the bird must have access to outdoor areas, the latter present a much bigger preventive challenge. Confinement was initially introduced for the control of the biosecurity level and to prevent passive and active disease transmission from wild birds and other animals. Today the required outdoor access, which in some European countries now account for more than 40% of the total egg production, places new demands for effective vaccines (Stokholm et al., 2010).

For some types of poultry, regarded as “minor species” *e.g.,* pheasants, ostriches and guinea fowl, the market is generally considered too small to commercially justify licensing of vaccines.

To fill these gaps autogenous vaccines are used to complement preventive strategies where no suitable commercial vaccines are available. They represent an important supplementary tool to secure animal health, prevent disease transmission, ensure consumer protection, and prevent significant economic losses.

3.1.4. Autogenous vaccines in poultry

As indicated above, several conditions justify the need of autogenous vaccines for poultry. Although the use of autogenous vaccines for poultry is the highest among all farm animals, the number of scientific reports detailing *e.g.*, modes of immunity and level of protection is very scarce. Due to the limited availability of commercially available licensed vaccines for poultry in general, the list of potential targets for autogenous vaccines is long (Table 1). Reports from the use of autogenous vaccines against *Escherichia coli* and avian Influenza virus seem to dominate, suggesting that these pathogens have been considered the most important targets for autogenous vaccines in the past.

Escherichia coli is one of the most frequent bacterial causes of disease across different species and age-groups of poultry (Stokholm et al., 2010; Poulsen et al., 2017; Naundrup ThØfner, 2019). *E. coli* occur commonly in healthy poultry flocks, where they are present in several antigenic variations, making development of broadly protective vaccines difficult. Although low pathogenic (LP) avian Influenza viruses (AIV) are uncommon in commercial poultry in Europe, AIV is highly prevalent in wild birds, particularly migrating ducks, and geese and therefore, the risk of introduction into commercial flocks is high. The ability of genetic reassortment provides AIV with a very high antigen repertoire, which due to poor cross-protection against heterologous AIV strains (McMillan et al., 2021) makes development of commercial vaccines highly challenging and highlights the necessity for autogenous vaccines to protect against LPAIV.

Overall, a crucial requirement for a successful prophylactic strategy is adequate flock profiling (Collett and Smith, 2020). Sequential collection of serological data and other disease and pathogen-associated diagnostic information should all be considered when the risk assessment for a specific farm or flock is evaluated, and the combined information is used to direct the best possible preventative measures.

Table 1: Examples of pathogens for which autogenous vaccines have been produced in the past

Bacterial pathogens	Specific targets for autogenous vaccines	References
Bordetella spp.	No available vaccine for poultry in Europe	
Brachyspira spp.	No available vaccine for poultry	Amin et al., 2009
Campylobacter spp.	No available vaccine for poultry	
Clostridium perfringens	No available vaccine for poultry in Europe	
Enterococcus spp.	No available vaccine for poultry	

Erysipelotrix rhusiopathiae	Lack of vaccines against certain serotypes	Stokholm et al., 2010
Escherichia coli	Limited or no cross-protection of licensed vaccines with circulating strains/serovars	Koutsianos et al., 2020; Li et al., 2017: Kromann et al., 2021; Landman and van Eck, 2017; Lozica et al., 2021a; Lozica et al., 2021b
Gallibacterium spp.	No available vaccine for poultry	
Pasteurella multocida	Licensed only for a limited number of poultry species but not for others	Kardos et al., 2007; Omaleki et al., 2020
Pseudomonas spp.	No available vaccine for poultry	
Riemerella anatipestifer	No available vaccine for poultry in Europe	
Salmonella serovars	Lack of vaccines against certain serovars	Davison et al., 1999 ; Groves et al., 2016
Staphylococcus spp.	No available vaccine for poultry	
Streptococcus spp.	No available vaccine for poultry	
Viral pathogens		
Avian Influenza viruses of various subtypes but H5 and H7	Limited cross protection between strains	Cardona et al., 2006; Fallah Mehrabadi et al., 2020; Gharaibeh et al., 2015; Kapczynski et al., 2009: Smietanka et al., 2014
Fowl adenoviruses (FAdV)	Limited availability not covering all FAdV-species	Alvarado et al., 2007; Gupta et al., 2018; Kumar

		et al., 1997; Schachner et al., 2021;
Infectious bronchitis virus	Limited cross reactivity against new emerging variants	Erfanmanesh et al., 2020; Ladman et al., 2002
Infectious bursal disease virus	Emergence of new virus variants showing little cross reactivity with licensed vaccines	Boudaoud et al., 2016
Reovirus	Lack of vaccines in some EU countries	Sellers, 2017
Rotavirus	No available vaccine for poultry	

This list does not claim completeness; including experimental studies on inactivated vaccine candidates.

3.1.5. Autogenous vaccines aimed at specific types of poultry

Commercial poultry production generally applies strict age-separation to avoid mixing of birds with different immune status and susceptibility towards common infectious pathogens. Similarly, different species of poultry are not mixed on most farms. Below, the main examples from different poultry production systems are provided.

3.1.5.1. Broiler breeders and broilers

Prevention of infectious diseases in broiler breeders is highly dependent on the breed and generally serve two purposes: 1) protection of the chicken from infectious diseases, 2) induction of maternal antibodies to prevent infections in the first weeks of life in the offspring. In fast-growing broiler lines, disease prevention may almost entirely be restricted to the rearing period of breeders, which, depending on the disease situation at the broiler production level, may only rely upon maternally derived antibodies. Reliance on passive immunity is only possible due to the short lifespan of the broilers and in cases where other preventive *e.g.*, high biosecurity standards and good hatchery management practices allow. For the slower-growing breeds, vaccinations are also needed during the broiler growth period. Particularly Infectious bronchitis virus, Infectious bursal disease and *E. coli* are some of the most common causes of infections in broilers, where autogenous vaccines are used to complement licensed vaccine. Commercial *E. coli* vaccines are available, yet due to the vast antigenic diversity within this species, which cannot entirely be accounted for by available vaccines, autogenous vaccines considering strains prevalent in specific farms or regions are also commonly used (Kromann et al., 2021; Lozica et al., 2021a;

Lozica et al., 2021b). To ensure adequate prevention against dominating pathotypes, continuous monitoring and detailed characterization of the lesions and their causes is critical. The use of whole genome sequencing of both bacterial and viral pathogens combined with databases and monitoring programs has allowed a targeted and dynamic approach towards limiting disease occurrence and need for antimicrobial use (Ronco et al., 2017; Bojesen et al., 2022).

3.1.5.2. Egg-laying chickens

Chickens laying eggs for human consumption are long lived and therefore need extended prophylactic measures to prevent infections. A recent investigation of approx. 7500 end-of-lay hens found *E. coli* as the major infectious cause followed by *Gallibacterium* (*G.*) *anatis* (Wang et al., 2019). As mentioned above, even though licensed vaccines against *E. coli* are used extensively, the antigenic diversity among *E. coli* affecting chickens may require additional vaccines to increase the protective breath. No licensed vaccine is available in Europe against *G. anatis*, which has led some to use autogenous vaccines against this organism.

Particularly the egg-laying industry is changing from having been based almost entirely on battery-cage and confined indoor systems, to free-range and organic systems where the chickens must have access to outdoor areas. That has dramatically changed the risk of exposure to pathogens originating from the soil and wild birds and other animals. Inability to keep biosecurity standards at a reasonable level in these production types have re-introduced agents like *Erysipelotrix rhusiopathiae* and *Pasteurella multocida* that largely have been absent for decades (Stokholm et al., 2010). The limited importance of these organisms for years is likely responsible for the fact that the available licensed vaccines have been on the market for substantial amounts of time (decades) and therefore may not reflect the current strains in the field (Opriessnig et al., 2020). In these cases, substitution or addition of autogenous vaccines surely have a role to ensure adequate protection (Mazaheri et al., 2005; Kaufmann-Bart and Hoop, 2009). Another challenge arises from an interest in keeping the egg-laying hens for more than one production cycle by letting them go through a moulting period and initiate yet another production cycle after that. For these birds living 100+ weeks, there may be a need for revaccination with both licensed and autogenous vaccines.

3.1.5.3. Turkeys

Turkeys can be considered as minor species based on the worldwide perspective. Therefore, only a limited number of vaccines is available. In many countries, commercial vaccines are available against Haemorrhagic enteritis, Newcastle disease and eventually turkey rhinotracheitis and used for routine immunization of fattening

turkeys. Depending on the housing type (including closed housing versus free-range), region and lifespan (fattening turkeys versus breeders) other important pathogens such *Escherichia coli*, *Bordetella avium*, *Erysipelothrix rhusiopathiae, Riemerella anatipestifer, Pasteurella multocida*, *Ornithobacterium rhinotracheale*, *Clostridium* species or viruses including Influenza-, Reo-, Picorna- or Adenoviruses may significantly affect the flock health. Depending on the epidemiological situation *e.g.,* proximity of the turkey houses to other poultry species or farm animals, other pathogens may need to complement this list (for example Bisgaard's taxa; *Mycoplasma* species against which vaccines have been licensed for chicken only).

In some countries, commercial vaccines may be available against some of these pathogens, but there is an overall need for autogenous vaccines against some or all these pathogens for turkeys throughout Europe. Due to the long lifespan of fattening turkey of up to 22 weeks and the value of the individual vaccination by injection with priming and booster of individual birds is also economically justified. Autogenous vaccines for turkeys may be based on monovalent as well as polyvalent products, which may include antigens of more than one pathogen. Autogenous vaccines for turkeys may need to be adjuvanted with different products compared to chickens to mount a protective immune response. It has been suggested that growing turkeys may mount a less prominent immune response than chickens against some pathogens, and therefore stronger adjuvants may be favourable, for example aluminium hydroxide or oil-based adjuvants.

For some pathogens, autogenous vaccines may not provide sufficient protection including *Histomonas meleagridis* (Hess et al., 2008) especially if protective immunity has to be cell-mediated. Therefore, autogenous vaccines are a very important tool to control disease in turkeys, but not applicable to all circulating pathogens. More research is required to better understand the protective immune response of turkeys as well as discover new adjuvants to overcome the obstacles of insufficient protection.

Continuous monitoring of commercial turkey flocks is necessary to detect circulating pathogens including NDV and TRT, against which commercially available vaccine are used, to identify antigenic variants or new subtypes, which may escape the immune response induced by the vaccine virus strains (Bello et al., 2018). If these are detected and insufficient immunity is confirmed for example by cross-neutralizing test, there may be a need for the development of alternative autogenous vaccines. This would help to close the gap between the newly emerging pathogens and the final release of a licensed new vaccine. Certainly, this approach holds true also for autogenous vaccines, for which a laboratory confirmation of the induction of pathogen-neutralizing antibodies would be desirable, and if new emerging strains are detected autogenous vaccines need to be strain-adapted. Therefore, the duration of the immunization period of an autogenous vaccine against a specific field isolate must be limited.

3.1.6. General considerations regarding use of autogenous vaccines in poultry

A recurring challenge is preventing several co-occurring pathotypes, which suggests the requirement of using multivalent autogenous vaccines (Galapero et al., 2019). This has been the case for example, where different variants of reoviruses apparently kept causing disease (Sellers, 2017). Similar approaches are used to prevent disease from different serotypes of *E. coli*. There is, however, little information available on possible limitations with respect to the number of pathogens/antigens that can be effectively included in a polyvalent vaccine for poultry. In human medicine, particularly paediatric medicine, vaccine interactions and antigen overload have been investigated yet no general conclusions in favour or against the use of polyvalent vaccines were made (Insel, 1995). Interference between vaccine components leading to a less effective protection has been described yet fully effective multi-valent vaccines considering up to 23 serotypes have also been found highly effective (Gregson and Edelman, 2003). For most small poultry species, the volume/dose may however represent a more important limiting factor than the number of antigens included (Gagic et al., 1999).

Broiler breeders and egg-laying chickens receive multiple vaccinations including autogenous vaccines during their rearing period. Here is a clear need for continuously updated knowledge on the currently dominating pathogenic species not covered by commercially available or missing adequately protective potential.

Autogenous vaccines may also be produced to protect other minor species including waterfowl, such as ducks and geese, as well as game birds or pigeons. Depending on the availability of vaccines waterfowl may be vaccinated for example against *Coenonia anatina*, *Pasteurella multocid*a or *Riemerella anatipestifer* or Duck Hepatitis Virus 1. In homing pigeons, the emergence of pigeon rotavirus A, has led also to the successful application of autogenous vaccines in countries where no commercial vaccines were available.

Independent of the type of poultry, new pathogens emerge which may require interventions that cannot await licensing of a vaccine. Recent examples are *Enterococcus cecorum* (Jung et al., 2018) and *Campylobacter hepaticus* (Crawshaw, 2019) where autogenous vaccines may represent a solution although only anecdotal evidence on their efficacy is available. Scientific data are, however, urgently needed to confirm the value of this type of intervention. The need is not restricted to these pathogens. Information of efficacy and safety of autogenous vaccines is often lacking and results from their use very rarely makes it into peer-reviewed journals available to a broad international readership. Evidence-based decisions are nevertheless crucial for improvement of current intervention strategies and for sustainable enhancement of the immunity of vaccinated birds, and for decisions on when to initiate and terminate of the use of a specific antigen(s) in an autogenous vaccine intervention.

3.1.7. Definition of the epidemiological unit

Production and use of an autogenous vaccine originally had to be based on a pathogen or antigen obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of the holding in the same locality (EU Directive 2001/82/EU). For this reason, the term “farm-specific” vaccine has also been used for autogenous vaccines. Particularly in poultry, the limitation of use for the same locality has been a challenge. In most poultry operations strict age separation, adhesion to the all-in-all-out principle and a strong focus on preventing disease transmission between different generations of poultry are key to efficient health management. Breeding stock delivers hatching eggs to often large hatcheries, which again provide day-old offspring to production units. Breeding, rearing and production farms may not belong to the same owner or/and may be positioned at distant geographical locations. In some instances, disease prevention, particularly in cases where vertical transmission occurs, is warranted across localities to ensure the best possible effect. This is particularly true in countries or regions where few, but large hatcheries supply the majority of day-old progeny to that country or region. Here it makes more sense to consider the epidemiological links between units rather than locality. It may thus be useful to use inactivated autogenous vaccines in poultry units that are geographically distinct (and sometimes far away from each other) but being part of the same breeding, rearing or production chain and linked by the movements of animals. Besides these structural characteristics of poultry production influencing the decision process with respect to the definition of the epidemiological unit, pathogen characteristics must be considered as well to account for transmission rates and modes. Highly volatile pathogens may affect several farms easily, while others may be restricted to individual barns.

3.1.8. Future perspectives

There is no doubt that autogenous vaccines represent an essential tool for the implementation of successful prophylactic strategies in poultry. However, they cannot replace the continuous need for licensed vaccines, which must pass a highly regulated, and time-consuming approval process focusing on safety, efficacy and stability as require by the European Pharmacopoeia. Nor will the need for rigid biosecurity measures disappear for some production systems.

To improve the efficacy of autogenous vaccines there is an urgent need to promote research on new and suitable adjuvants as well as antigen-preparation protocols for this type of vaccine. Focus on the evaluation of the efficacy of this type of vaccines in the field is also an area that would benefit substantially from transparent protocols. This is important to ensure continuous support of these vaccines and to justify the use of complex multivalent vaccines for poultry. Reports from field experiences should to a higher extend find their way into scientific literature to provide the basis for decision-

making processes of veterinary authorities in disease control.

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3.2 Autogenous Vaccines for Pigs

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Swine farms show a high variation in biosecurity conditions, production systems, supply relationships and proficiency levels, so that farm-specific vaccination protocols must be elaborated by farmer and advising veterinarian. The high economic pressure in pork production has to be taken into account prior to the decision for implementation of a vaccine.

Against most obligate and important secondary pathogens in swine, commercial vaccines are available. Especially for respiratory diseases all obligatory pathogens as *Actinobacillus pleuropneumoniae*, *Mycoplasma hyopneumoniae*, PRRSV, PCV2 and Influenza virus A are covered. Respiratory disease in swine is multifactorial, and bacterial agents can either induce disease, pave the way for other infectious agents or lead to additive or synergistic effects during co-infections (Opriessnig et al., 2011). By systematic reviews and network meta-analyses of vaccination studies with commercial vaccines against bacterial respiratory pathogens estimates of their efficacy were performed, which resulted in wide confidence intervals. These findings mainly indicated beneficial effects but some harmful effects were also noted (Sargeant et al., 2019). A similar outcome of a network meta-analysis for effects of autogenous vaccines can be expected, because various factor constellations on a farm can prevent an adequate protectivity of the vaccine. Next to production and storage failures (contamination of vaccine, needles or syringes, incorrect storage at too high or too low temperatures or direct sunlight exposure, chemical or physical destruction of antigens during killing process), administration failures (individual animals inadvertently not vaccinated, faulty injection in subcutaneous fat) or the influence of biological factors (vaccine is not eliciting an adequate immunity, the pig is already in the incubation period when vaccinated, interference with maternal antibodies) can impact vaccine efficacy.

Commercial vaccines run through a tightly regulated licensing process and are checked for safety and protectivity under standardized experimental as well as field conditions. It can be expected that a commercial vaccine is superior to an autogenous vaccine due to new vaccine technologies and adjuvants used commercially (Chamba Pardo et al., 2021). The fact, that no commercial vaccine is available for a specific pathogen might be either due to the fact, that the market is assessed to be too small for the product or that it was not possible to develop a protective vaccine. In the latter case it would be questionable, whether an autogenous vaccine could fill this gap. Nevertheless, autogenous vaccines in swine medicine are an important tool for practitioners, because they retain a capacity to act. A literature survey resulted in only

a small number of published field studies. Empirical knowledge, former experiences or the urgent need to act are the main drivers for the use of autogenous vaccines, which can be considered as experimental vaccines, that must not meet efficacy standards.

Finally, also recommendations for implementation of autogenous vaccines should be science-based and after the respective pathogenic organism has been identified in combination with evidence of being the cause of disease. The cost of the vaccine should not be a criterium in selecting an autogenous instead of a commercial vaccine, because production data, morbidity, mortality are finally decisive for the cost-benefit outcome.

The draw-back of the lack of knowledge on protectivity and safety in autogenous vaccines is balanced by their flexibility. They are an important tool for herd health management in cases, when no commercial vaccine against a pathogen is available, when pathogen subtypes and therefore antigenic variation occur, so that there is a need to widen the spectrum of protection.

Historically, first autogenous vaccines were administered orally for maternal immunization of sows (Parvovirus, TGE, *E. coli*) to induce mucosal immunity in the gut, as the basis for high maternal antibodies in colostrum and milk to protect off-spring. These oral autogenous vaccines were highly effective against intestinal diseases.

Autogenous vaccines against respiratory tract pathogens (e.g. *Pasteurella multocida* type D, *Bordetella bronchiseptica*) were administered intramuscularly, or subcutaneously and were not fully protective although containing adjuvant (e.g. aluminium hydroxide).

3.2.1 General and legal aspects of autogenous vaccines in swine

In Section 3 Article 106 (5) of the EU regulation 2019/6 it is clearly defined, that an autogenous vaccine can only be used, if no immunological veterinary medical product is authorised for the target animal species and the indication.

This raises the question of a clear definition of an indication. Under field conditions a complex interaction between environment, host and different commensal, environmental and pathogenic microorganisms can be observed, which are decisive for disease pathogenesis. In most cases not only one single pathogen is involved in disease pathogenesis and often several strains of one bacterial species can cause the clinical picture. Multifactorial disease and mixed infections can be an indication for the design of a farm-specific autogenous vaccine, so that including different pathogens in one vaccine can be reasonable. An indication must be therefore defined for every farm

individually and can vary between farms although the spectrum of pathogens is overlapping in parts.

It has to be decided from case to case if an isolated strain with specific characteristics and virulence factors is an indication for the implementation of an autogenous vaccine although a commercial vaccine against the respective bacterial or viral species is available. In case that the detected strains vary from those in commercial vaccines, the production of an autogenous vaccine can be justified. In case, that differentiation of strains is not possible due to lacking diagnostic methods, the clinical outcome of any vaccination strategies should be documented in detail.

The veterinarian is responsible for assessment of the success after implementation of any vaccine. So far, no correlate of protection for autogenous vaccines is available, which can be measured by laboratory methods. Therefore, the swine practitioner has to rely on production data and his clinical examination to evaluate the implemented measures by the clinical outcome.

Additionally, the pathogens used shall be obtained from animals in an epidemiological unit and only used for animals in the same epidemiological unit or the treatment of animals in a unit having a confirmed epidemiological link (Chapter 1, Article 2 (3), EU Reg. 2019/6). Regarding the epidemiological unit, the definition is based on point (39) of Article 4 of Regulation (EU) 2016/429. It says: “epidemiological unit means a group of animals with the same likelihood of exposure to a disease agent”. Therefore, the definition of an epidemiological unit/link has to be decided by the attending vet in each individual case as it is a difference if the used pathogen is easily transmitted by air, or needs direct animal to animal contact. The clearest epidemiological link regarding pig production can be found in a direct piglet producer/fattener cooperation (Fig 1), when the piglet producer already vaccinates the piglets with a pathogen isolated at the fattening unit to protect the piglets before entering the fattening units.

Epidemiological links between production systems that have different owners and obtain animals from each other, sometimes alternating.

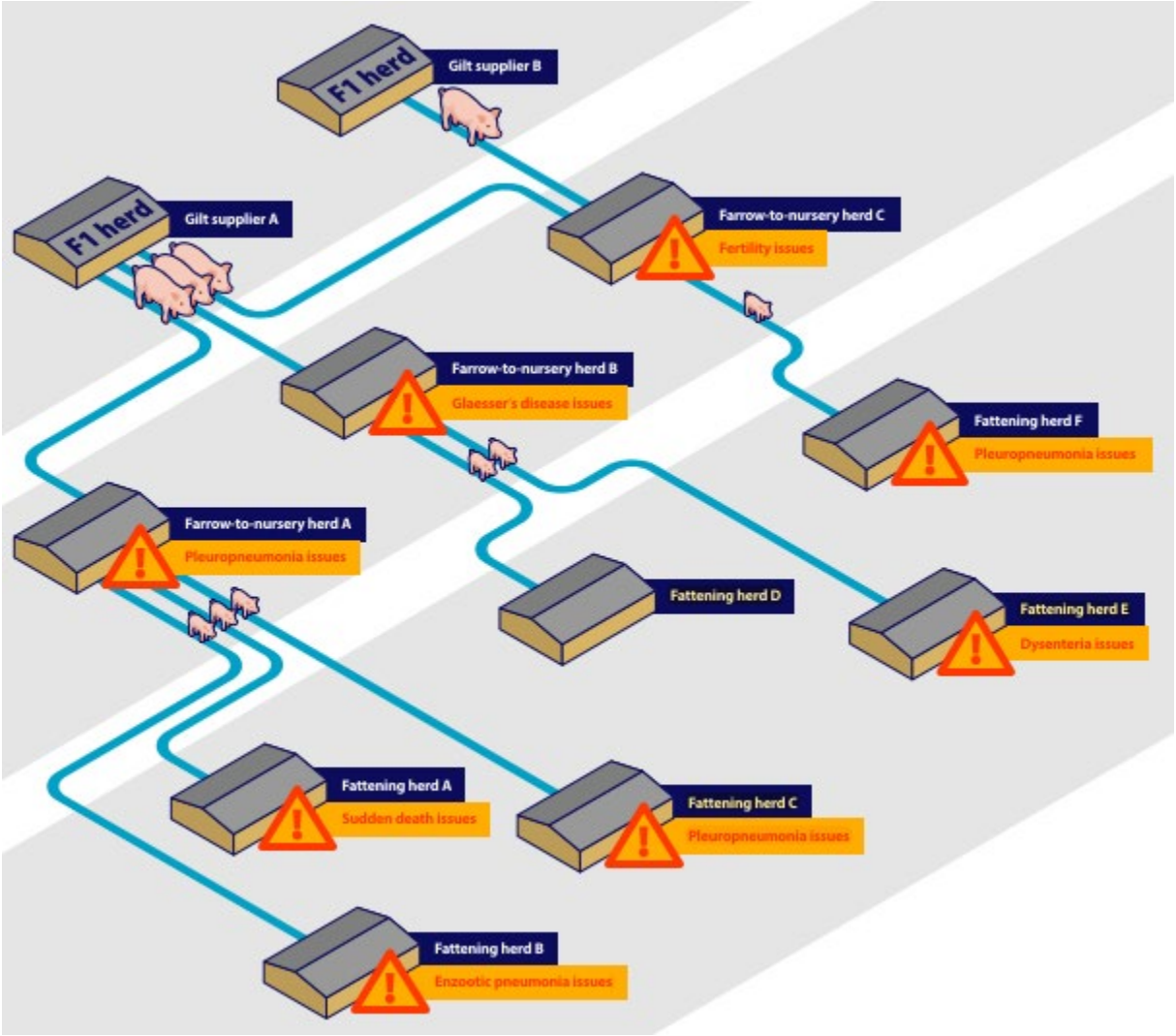

Fig. 1: In this example all farms belong to different owners. The sourcing of animals is variable. Implications of the pathogens are dependent on their occurrence and other factors like hygiene measures, the overall management and the synergistic pathogen profile in the individual herd.

While the epidemiological unit is specific for the farm or the production chain, the epidemiological link has to be defined including the specific pathogen characteristics with respect to infection and transmission dynamics. To define a respective epidemiological link, the following pathogen categories should be assessed separately:

- pathogens transmitted by air (e.g. influenza virus)
- pathogens transmitted mainly by aerosols (e.g. *Actinobacillus pleuropneumoniae*)
- pathogens transmitted by direct or indirect animal-to-animal-contact (e.g. *Salmonella spp.*)
- pathogens transmitted vertically (e.g. PRRSV).

The epidemiological link is relatively clear in supply chains from farrowing farms to nursery pigs and fattening pigs (Gilt supplier D- Farrow-to-nursery herd A- fattening herd B) as shown in Fig. 2. With respect to specific pathogens in this example, the epidemiological link can be concordant with the epidemiological unit (e.g. salmonella).

The complexity of definition of the epidemiological link is shown in Fig. 1, when only one fattening farm (fattening herd E) out of two fatteners suffers from a specific disease. It can be discussed, when the farrow-to-nursery herd B is allowed to vaccinate all piglets irrespective of the fattening farm to which they will be later delivered. In order to reduce the bacterial burden already in the farrowing farm and due to practicability reasons (not possible to separate piglets in groups of vaccinated and non-vaccinated piglets), vaccination of all piglets seems to be meaningful. Due to the fact that vaccines are expected to be safe and have a beneficial effect on animal health, it should be possible in these complex cases to vaccinate all piglets in farrowing farm B.

Epidemiological links in closed production systems with one owner or with stabile exchange of animals.

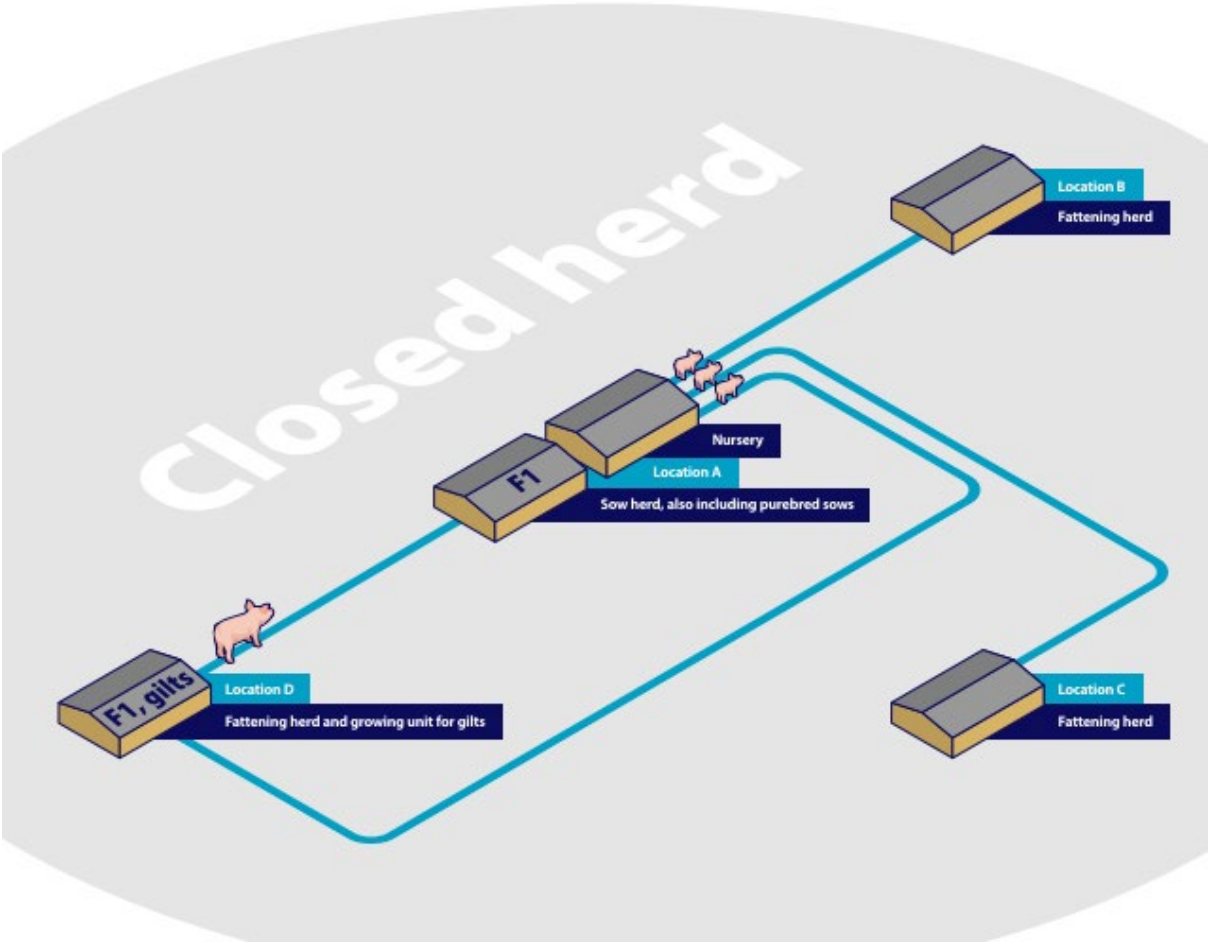

Fig. 2: In this example all farms belong to one owner. One system hosts the purebred animals, F1 gilts, sows, nursery and fattening pigs. Exchange of animals takes part only between the different parts of the system. Pathogens can occur endemically and circulate in the system. Hence in certain cases the system can be considered as epidemiological unit with similar risk of infection.

The swine practitioner who is in contact with the farmer and knows the different production stages, is obliged to examine the animals prior to taking measures and assess the infection dynamics within the production chain. He has to diagnose the

pathogens involved and other factors comprising the disease pathogenesis. Finally, the practitioner has to decide together with the farmer, the optimum preventive measures. In case of the implementation of an autogenous vaccine, the swine practitioner is fully responsible for fulfilment of good veterinary practice within the legal framework.

3.2.2 Autogenous vaccines used in swine

Autogenous vaccines are inactivated bacterins containing marginal adjuvant, so that frequent revaccination (4-6 month intervals) is necessary. In general, a basic immunisation generally in an interval of 3-4 weeks is necessary.
In many cases multiple antigens are combined in one vaccine without any information about the impact of adjuvant-pathogen combination or potential antagonistic effects. Usually the minimal concentration of antigen required to provide adequate protection is not known due to a lack of antigen titration studies and experimental animal protection trials. It can be assumed, that higher numbers of different antigens included in the vaccine, reduce the concentration of the single antigen.

These autogenous vaccines are used although commercial vaccines are available against the respective species:
E. coli
Clostridium perfringens A
Actinobacillus pleuropneumoniae
Glaesserella parasuis (only serotypes 4 and 5 in commercial vaccines)
Pasteurella multocida
Porcine Influenzavirus A
Bordetella bronchiseptica (in commercial vaccines the main indication is atrophic rhinitis)
Erysipelothrix rhusiopathiae

These autogenous vaccines are implemented because no commercial vaccines are available against the respective species:
Mycoplasma hyorhinis
Mycoplasma hyorhinis
Mycoplasma hyosynoviae
Streptococcus suis
Rotavirus A
Staphylococcus hyicus
Porcine influenza virus A H1pdmN2
Clostridium difficile
Streptococcus dysgalactiae
Brachyspira spp.

Autogenous vaccines against pathogens rarely involved in diseases, where no commercial vaccines are available:

Actinomyces hyovaginalis
Truerperella abortisuis
Staphylococcus chromogenes
Streptococcus gallolyticus
Salmonella Choleraesuis (commercial vaccine not available anymore)
Salmonella Derby
Salmonella Livingstone
Staphylococcus aureus
Trueperella pyogenes
Enterococcus hirae
Porcine Teschovirus Type 1
Pasteurella mairii
Klebsiella pneumoniae
Actinobacillus suis
Streptococcus alactolyticus
Enzephalomyocarditis virus

3.2.2.1 Actinobacillus pleuropneumoniae (A.pp.)

After infection with *A.pp.,* convalescent animals are considered to be protected against the homologous serotypes and partly also against heterologous serotypes (Cruijsen et al., 1995). From the laboratory studies performed by Nielsen between 1974 and 1995 is known, that protective immunity of convalescent animals differ after infection with a heterologous serotype. Pigs infected with serotype (ST) 2 were protected from clinical symptoms after challenge with ST 1, 2, 4 and 5 three weeks after first exposure (Nielsen, 1979). While cross-protection was also shown after infection from heterologous serotypes, this was not the case after vaccination.

Infected pigs were shown to have a higher response in delayed-type hypersensitivity (DTH), antibody response and avidity against major antigenic components of *A.pp*., especially against the Apx toxins (Furesz et al., 1997). These findings indicated towards a better **cell-mediated immune response** after infection, which was not induced after vaccination. Production of antibodies is dependent on T-helper cell activity, which was reflected by the measured DTH. It is known so far that gamma-delta T cells CD8+ and TH17 cells (CD4+CD8αdimIL17A+) are involved in cell-mediated immune response after infection (Faldyna et al., 2005; Sassu et al., 2017).

Another important difference between infection and vaccination is the route of pathogen exposure, which is decisive for development of **mucosal immunity**. To elicit

mucosal immunity *A.pp*. bacterins have been administered via aerosol and orally under experimental conditions. Improvement of local, mucosal immunity mediated by specific IgA, IgM and IgG was achieved not only in blood, but also on mucosal surfaces (Hensel et al., 1994; Hensel et al., 1995a; Hensel et al., 1995b).

Next to mucosal immunity **neutralising IgG antibodies against Apx toxins** are highly relevant for protection and also provide protection of piglets by maternal colostral antibodies (Bosse et al., 1992).

Early vaccination experiments with killed *A.pp.* administered intramuscularly resulted in definition of optimal growth conditions for vaccine production. It was possible to protect 90% of vaccinated pigs after a homologous challenge. The respective bacterin was an inactivated *A.pp*. culture grown for 6 hours and administered in combination with Freund´s incomplete adjuvant (Nielsen 1982). The time-point of killing cultures during vaccine production as well as the adjuvant used were important factors for protectivity of bacterins. A 6-hour culturing was found to be more appropriate than a 24-hour culturing, and Freund´s incomplete adjuvant was superior to an aluminium hydroxide gel with respect to protection, but neglecting the severe local reactions (Nielsen, 1976). Producers of these early autologous *A pp*. vaccines recommended 10^9 killed bacteria per millilitre vaccine and an incubation period less than 6-8 hours to minimize production of toxic components. For the same reason, the number of different *A.pp*. serotypes in one vaccine is limited to minimize toxic effects by large amounts of endotoxins released by gram-negative bacteria (informal information by Dr. Sebastian Bunka). Endotoxins in autogenous vaccines can cause lower average daily weight gain after vaccination due to stress and toxic effects (endotoxins/lipopolysaccharides). Major draw-backs of *A.pp*. bacterin vaccines are their intramuscular route of application, which does not reflect the natural route of infection, and a lack of bacterial products in the vaccine, which are important antigens for protection (e.g. Apx toxins).

Using a four-fold bacterin containing St 1,3, 5 and 9 protected against challenge with homologous serotypes resulting in less lung lesions and greater daily weight gain in vaccinated animals (Tarasiuk et al., 1994). Protection was incomplete and vaccinated pigs were still carriers of *A.pp*. A bacterin containing ST1 and 5 was successful in protection against homologous challenge, but only if vaccinated two or three times in two-week intervals. Mortality as well as chronic lung lesions in week 10 after challenge were prevented by vaccination, but not clinical symptoms 36 hours after challenge (Higgins et al., 1985).

Challenge with heterologous *A.pp*. after bacterin vaccination was not successful. Pigs vaccinated with a killed ST2 vaccine were not protected after challenge with ST 1, 5, 6 or 8 and pigs vaccinated with ST 4 or 5 were not protected after challenge with ST 2 (Nielsen, 1984). It was also shown, that a vaccine containing ST 1 to 6 was protective

against ST8, which has overlapping antigens with ST3 and 6.

Already from these early experiments it became clear, that specific IgG mediates protection against severe clinical symptoms, that mucosal immunity is decisive for prevention of mucosal damage, that the carrier status of pigs cannot be prevented by vaccination with bacterins, and that basic vaccination must be performed twice in an at least two-week interval. *A.pp.* bacterins protect against homologous challenge. Protection against heterologous infection with a ST belonging to the group of cross-reactive serovars (1-9-11, 3-6-8, 4-7) can be expected.

Empirical observations about effectivity of autogenous *A.pp*. vaccines have been summarized by authors involved in production of autogenous *A.pp*. vaccines about 30 years ago. They stated, that success of vaccination is highly variable. An *A.pp*. autogenous vaccine can be considered as successful, when morbidity is reduced by 20-40%, mortality by 60-80% and treatment incidence by 60%. An overall improvement in average daily weight gain, reduction in macroscopic lung alterations and protection of piglets up to the age of 3-8 weeks by maternal immunization can be expected (informal information by Sebastian Bunka).

Effective commercial *A.pp*. vaccines have been developed since the early cross-protection trials of the group of Nielsen in the end of the last century, which provide cross-protection against most serotypes. The fact, that protectivity also of these commercial vaccines can vary in different farms might be due to the fact, that local immunity in the respiratory tract necessary to prevent adhesion of the pathogen, is not adequately triggered by vaccines administered intramuscularly. As the consequence of negative experiences with commercial vaccines, some veterinarians sidestep to autogenous vaccines but also with varying success rates. These field experiences are rarely published.

Prior to availability of the commercial *A.pp*. vaccines the protectivity of autogenous *A.pp*. bacterins have been proven under experimental conditions or in small groups of animals after homologous challenge (Pangerl et al. 1986). In most reports bacterin vaccines were found to be protective under field conditions (Pangerl et al. 1986, Kielstein et al. 1982, Mason et al. 1982).

In low numbers of animals, the effect of autogenous *A.pp*. vaccines containing different adjuvants were tested under field conditions. A positive effect with regard to mortality and morbidity was shown (Rosendal et al., 1981). One vaccine contained peanut oil, arlacel 80, tween 80 as an adjuvant, while the other contained aluminium hydroxide. After initial vaccination systemic side effects as vomiting were observed.

Sporadic but unspecific comments about the efficacy of autogenous vaccines can be

found in agrarian magazines. In the case of disease caused by certain *A.pp*. serotypes and after the failure of commercial vaccines, vaccination with *A.pp*. autogenous vaccine is recommended (Gottschalk, 2017). Failure of *A.pp.* bacterins was assigned to antibodies directed against the outer membrane peptidoglycan-associated lipoprotein PalA, which can counteract protective antibodies against Apx toxins and lead to severe courses of infection. Variable effects of autogenous vaccines might be due to variable PalA levels in the vaccine (Liu et al., 2017; van den Bosch and Frey, 2003; Van den Wyngaert et al., 2015).

3.2.2.2 Streptococcus suis

The important pathogen *Streptococcus* (*S.*) *suis* affected mainly weaned piglets worldwide. About 35 serotypes have been described and the protective antigens are not known so far. No licensed vaccine is available in Europe, so that autogenous vaccines are sometimes used for prevention of disease. Various different strains can be detected in one farm and within one animal and many isolates remain untypable. The fact that various different strains can cause disease in one herd that might be detected in normally sterile body sites, such as brain and joints complicates the selection of strains for effective autogenous vaccines. Serotype 2 and 9 are the most prevalent invasive ST in Europe. European virulent ST 2 strains are often positive for genes encoding suilysin (haemolysin), muramidase-released protein and their extracellular factor. Due to the high diversity of strains within one ST sample, numerous affected pigs should be analysed and typed to obtain all different invasive isolates. Herd problems caused by more than four different *S. suis* genotypes, as well as by mixed infections with *Glaesserella* (*G.*) *parasuis* have been recorded (Rieckmann et al., 2020).

The high impact of pre-disposing factors on disease development in already colonized pigs is reflected by the varying outcome of published vaccine efficacy studies in the field. In most studies, vaccine efficacy varied over time, so that the final assessment of authors is that *S. suis* cannot or cannot totally be controlled by vaccination (Torremorell et al., 1997). Next to analysis of herd factors, in-depth typing of isolated strains causing disease can help to assess the potential benefit of vaccination. In case that multiple different genotypes can be detected, pre-disposing factors are decisive for disease pathogenesis. This would reduce the likelihood of a protective effect of an autogenous vaccine. It is assumed that the herd status for porcine reproductive and respiratory syndrome and influenza virus infection and the occurrence of certain *S. suis* pathotypes are decisive for outcome of immunoprophylaxis with autogenous bacterins. An instruction for the management of expectations for the efficacy of an autogenous vaccine is described in detail by Rieckmann et al. (2020). The overall effectiveness of autogenous vaccines cannot be stated so far. In a recent systematic field trial 75% of the piglets per litter were vaccinated in five cohorts, one day before weaning and three

weeks later in the nursery. Total and overall vaccine effectiveness calculated by Cox's and logistic regression was 27% and 21%, respectively (Hopkins et al., 2019).
For the production of autogenous vaccines, only invasive isolates harvested from usually sterile body sites of diseased pigs should be used. *S. suis* ST 2 bacterins elicited protection against homologous challenges (Baums et al., 2010; Baums et al., 2009). Not all ST2 vaccines are considered to be protective and water-in-oil adjuvant was superior to aluminium hydroxide adjuvant (Wisselink et al., 2001). The time-schedule of vaccination was also decisive for protection, as prime-boost vaccination with a ST2 bacterin was not protective in early vaccinated piglets, but earliest after weaning (Baums et al., 2010; Baums et al., 2009). Because of interference with maternal antibodies, pigs should not be vaccinated prior to 3-4 weeks of age (Haesebrouck et al., 2004). No studies have been performed to determine the efficacy of multivalent S. suis bacterins so far. A risk of interference in elicited immune responses might exist.

S. suis ST9 bacterin prime-boost vaccination in the 4th and 6th week of life was successful to protect after experimental homologous challenge, although pigs developed an endocarditis (Büttner et al., 2012). Efficacy of autogenous ST9 vaccines might be restricted, because ST9 strains are biofilm producers and are protected from opsonophagocyting antibodies. Overall, autogenous ST9 bacterins are known to be less effective than ST2 bacterins (Rieckmann et al., 2020).

Only partial protection was found for a ST7 autogenous vaccine applied after weaning (Unterweger et al., 2014). Another vaccination study using a ST7 vaccine in pre-parturient sows and replacement gilts resulted in increases in anti-*S. suis* total antibodies in sows and in their piglets up to day 7 of age. Observed maternal immunity did not last beyond the post-weaning period and clinical findings were not evaluated in this study (Corsaut et al., 2021).

For a ST14 bacterin used for pre-farrowing vaccination of sows, a positive effect on frequency of neurological signs in 13-day-old piglets after homologous challenge was found. No difference with respect to the incidence of bacteraemia, lameness or mortality was found between piglets from vaccinated and non-vaccinated sows (Amass et al., 2000).

The induction of opsonizing antibodies by an autogenous vaccine would suggest its protectivity. So far, this test is not routinely performed (Rieckmann et al., 2020). As *S. suis* escapes the immune system by survival and multiplication in monocytes, antibodies might not be able to inactivate the microorganism (Williams, 1990). Finally, simulating cell-mediated immunity would be a goal for further vaccine development, which cannot be achieved by killed vaccines using conventional adjuvants and injection routes.

The importance of early exposure of piglets for development of a protective immunity, was shown in a study in which 5-day-old baby pigs were inoculated on their tonsils with a pathogenic ST2 endemic in the herd. The measure significantly reduced clinical signs later in life (Torremorell et al., 1999).

3.2.2.3 Staphylococcus hyicus

Practitioners frequently use autogenous vaccines to prevent exudative skin infections. The efficacy of vaccinations to protect piglet herds faced with sudden development of disease, was assessed to be high. Maternal pre-farrowing vaccination was also found to be successful in protection of piglets by transfer of specific IgG.

A sow herd vaccination scheme with prime-boost vaccination of all sows in a three weeks interval and revaccination every 6 months was implemented successfully on three different farms. It was possible to prevent exudative epidermitis in piglets during the years, when sow vaccination was performed (Sieverding, 1993).

In another field study, nursery piglets affected by exudative epidermitis and three different *Staphylococcus hyicus* isolates positive for the *exh*B gene encoding for the exfoliative toxin type B (ExhB) were used for vaccine production. Sows were vaccinated two-times in a three-week interval pre-farrowing. After implementation of the vaccination protocol morbidity, mortality and antimicrobial usage were significantly reduced (Arsenakis et al., 2018).

3.2.2.4 Glaesserella parasuis

Even vaccination with the same serovar of Gps can lead to divergent cross-protection after infection with different strains belonging to the same serovar (Costa-Hurtado et al. 2020). Using autogenous vaccines based on several strains present in a farm, variable and lower concentrations of antigens can lead to failure of protectivity. Vaccination of a subgroup of sows with an autogenous Gps vaccine resulted in elevated anti-Gps antibodies in suckling piglets, which were not correlated with colonization (Kirkwood et al. 2001). Autogenous sow vaccination with ST 5, 12 or nontypable *Glaesserella parasuis* (*Gps*) to prevent Glasser's disease in weaner pigs was successfully implemented in two large swine farm systems, where sows were vaccinated 5 and 2 weeks before farrowing. Mortality rate could be more than halved in nursery pigs. The authors recommended strain typing for *tbp* (transferrin binding protein) genes to identify potentially protective strains (McOrist et al., 2009). In general, vaccination of sows prior to farrowing is an important tool to control Glässer´s disease. Piglets are protected during lactation and -if vaccinated prior to weaning again-also in the nursery if the relevant strains are included in the vaccine. To achieve this is the major challenge in vaccine composition (Costa-Hurtado et al. 2020). The lack of a

multivalent vaccine is mostly the cause for disease outbreaks in vaccinated animals. A further drawback of autogenous vaccines is the necessity for multiple immunizations to generate long-term protection (Liu et al. 2016). In a field study the controlled exposure of pigs by a low dose of living Gps showed a higher protectivity than commercial or autogenous vaccination of pigs (Oliveira et al. 2003). While two strains were included in the autogenous vaccine, three strains were used for exposure. The lack of protectivity after vaccination was explained by a better induction of homologous mucosal immunity by exposure, which is finally preventing pathogen systemic invasion.

3.2.2.5 Mycoplasma hyosynoviae

So far, there are contradictory reports about efficacy of autologous vaccines against *Mycoplasma* (*M.*) *hyosynoviae.* It cannot be stated whether the use of autogenous vaccines is sufficient in preventing disease (Thacker and Minion, 2019). Due to a lack of commercial vaccine for prevention of disease caused by *M. hyosynoviae* autogenous vaccines are used in fatteners and gilts. Lameness in growing pigs can be a multifactorial problem with *M. hyosynoviae* being only one factor.

In a case report a *M. hyosynoviae* strain isolated from the joint of a diseased swine was used for production of an oil-in-water bacterin for vaccination of replacement gilts twice at 12 and 15 weeks of age. In vaccinated gilts, the culling rate due to lameness decreased significantly (Luehrs and Pabst).

3.2.2.6 Brachyspira hyodysenteriae

Little scientific evidence exists for the efficacy of autogenous vaccines against *Brachyspira* (*B.*) *hyodysenteriae.* In a comparative field study half of the pigs were vaccinated in week 6 and 9 with a vaccine containing three inactivated *B. hyodysenteriae* strains with aluminium hydroxide as adjuvant. Differences between vaccinated and non-vaccinated pigs with respect to mortality and average daily weight gains were not significant (Neirynck et al.).

So far, a benefit of autogenous vaccination against *B. hyodysenteriae* was not reported.

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3.3 Autogenous Vaccines for Cattle

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3.3.1 Introduction

Although tremendous progress has been achieved in management and technology of cattle production systems, animals still succumb to infectious diseases mostly multifactorial by origin (e.g., neonatal diarrhoea and bronchopneumonia in calves). Although the usage of antimicrobials to combat infectious diseases has been declining in recent years, still substantial amounts of antibiotics are administered to cattle bearing the risk of induction of antimicrobial resistance (Saini et al., 2013).

Herd health rests on six pillars: 1st Nutrition, 2nd Parasite control, 3rd Biosecurity, 4th Vaccination, 5th Genetics and 6sth Stress Management (Navarre, 2020). Neglecting one of the areas cannot be fully compensated by improvements obtained in another field. Today, preventive veterinary health services on dairy and beef cattle farms include consultancy for improvement of nutrition, housing conditions and management as well as for the design of strategic control programs to combat infectious diseases on basis of on-farm risk assessments. Vaccination against putative causal pathogens forms a simple and effective way of protecting animals (Young, 2019). The natural defence mechanisms of the organism are triggered to build resistance to specific infections. To this end, vaccines form an important element to eliminate or alleviate clinical disease caused by infectious agents in individual populations of cattle. There is now evidence from epidemiological studies that vaccines directed at infectious pathogens can induce non-specific immunomodulation additional to induction of a specific immune response; the mechanism has been shown to be related to induction of cross-reactivity of the innate immune system through epigenetic reprogramming (Benn et al. 2013). The consequences, however, can be beneficial but also detrimental as reflected in unwanted side-effects. Further research is warranted to explore these effects.

A great number of commercial vaccines are available addressing a broad spectrum of relevant infectious agents posing risks to bovine health (Ständige Impfkommission Veterinärmedizin, 2021). REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC lays down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of veterinary medicinal products (EU, 2019) and is expanded by national regulations that prescribe the use of vaccines in food producing animals (Ständige

Impfkommission Veterinärmedizin, 2021).

Implementing strategies to improve the health status of farm animals requires profound knowledge of the epidemiology of specific pathogens as well as of the characteristics of the different production systems. The choice of the vaccine and the groups of animals that are immunized must be carefully selected. In addition, specific requirements of the different production branches and of the distinct farm must be considered when a vaccination strategy is adopted within a preventive health program. The vaccine selected, should be efficient against one or more agents that are most likely causing the disease (Pollard and Bijker, 2021). Depending on the level of biosecurity in the herd (closed versus open) the production branch and the pathogen most likely causing the disease adequate diagnostic sampling should be performed in outbreak situations (Arbeitskreis Antibiotikaresistenz der DVG, 2018). In addition, cost benefit considerations must be taken into account when introducing a vaccination strategy on a farm. Following Stokka and Goldman (2015) three principles should be considered when implementing a vaccination program: 1st necessity: the risk of exposure is high enough to cause clinical disease and pathogen transmission will lead to impaired well-being of the animals; 2nd efficacy: there is scientific or observational experience that vaccine selection for specific pathogens is effective in the herd; 3rd safety: is there evidence that vaccination will not cause harm? The same authors postulate that the aim of a vaccination strategy should not only be directed at the protection of single animals, but also at the reduction of individuals shedding the pathogen, decreasing the amount and the duration of pathogen shedding and increasing the pathogen load needed to cause infection.

In case commercial vaccines are not available or have been proven ineffective in the given situation autogenous vaccines form a valuable instrument in programs of herd health management (Ständige Impfkommission Veterinärmedizin, 2021). Autogenous vaccines, also termed self or custom vaccines, are produced from bacteria and viruses isolated from sick animals (O'Connor et al., 2019). Due to the usage in emergency situations and to be able to deliver the vaccine in an acceptable time frame and at economically justified costs, autogenous vaccines do not have to undergo a licensing procedure to obtain regulatory approval by national authorities. *Article 159* of the REGULATION (EU) 2019/6, however, requires for inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit, that these are 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. To this end, veterinarians who prescribe an autogenous vaccine are responsible for its administration in the field under the restrictions given (EU, 2019; Ständige Impfkommission Veterinärmedizin, 2021). An advantage of autogenous vaccines is the fact that herd-specific strains can be used. Such strains have been demonstrated to

differ from those included in commercial vaccines. In addition, combination of antigens can be used in an autogenous vaccine (Chase, 2004). A disadvantage of the latter vaccines is the risk of unwanted transmission of agents (for example agents that could cause TSE), or induction of an antibody response whenever subunits of agents that are subject of a national control program aiming at a “disease free” status (for example Bovine Herpes Virus-1) are present in the vaccine. In addition, while commercially available products undergo a challenge process in animal models to prove their efficacy to generate a protective effect against the agent they are directed at, this is not applicable to autogenous vaccines (Chase, 2004). To this end, as required by law the use of autogenous vaccines demands a thorough accompanying documentation and evaluation of the success of the vaccination for example in terms of data on morbidity and/or mortality in the herd. Information with respect to documentation of vaccination efficacy is given in the “Guidelines for measuring and reporting calf and heifer experimental data” by Kertz and Chester-Jones (2004).

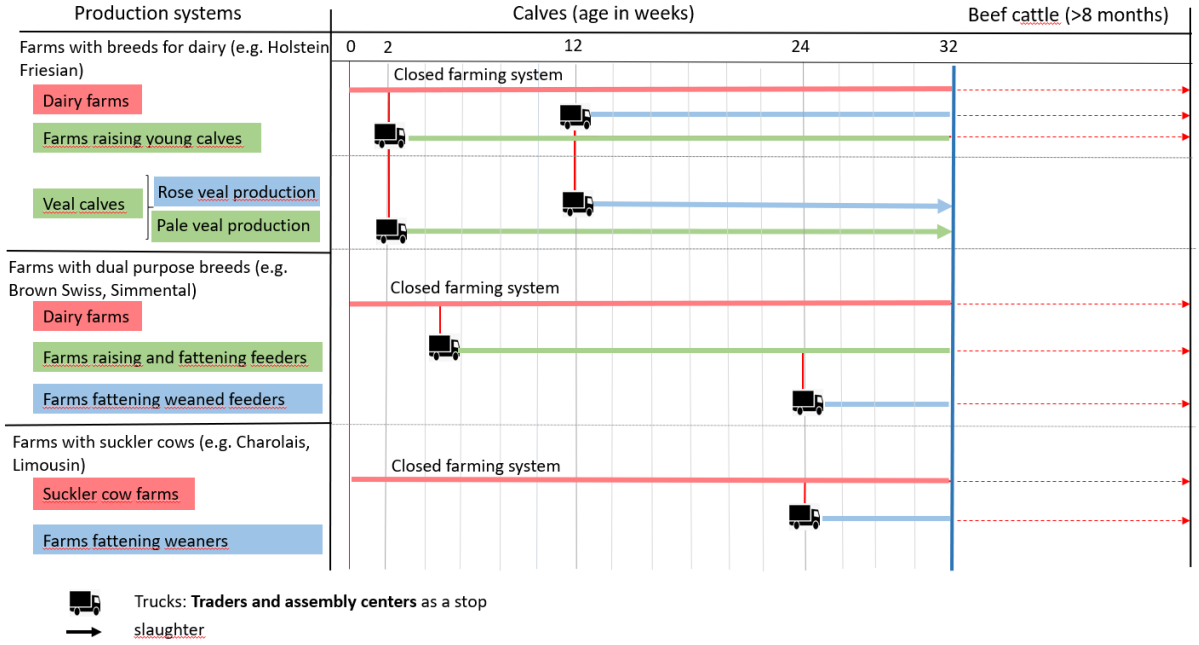
In veterinary epidemiology, the term “epidemiological unit” refers to a group of animals that is of epidemiological significance in terms of the transmission and maintenance of infection, and therefore of disease control; this term does not only refer to a single farm. Neighbouring farms with direct contacts between the animals, rearing farms and the receiving dairy farms, alpine pasturing, and further farms with close and verifiable epidemiological links fall under this term; in contrast, herds that are managed completely independently form separate epidemiological units (Thrusfield, 2005). Due to the great spectrum of farming systems dealing with the bovine species, the term “epidemiological unit” needs a closer consideration.

3.3.2 Categorization scheme for farms rearing calves for various purposes

Cattle production is a diverse sector comprising dairy and beef production in a broad spectrum of systems. To identify epidemiological units or epidemiological links within a production branch, a categorization scheme is needed, which illustrates the chain of sellers and buyers as well as animal movements within the distinct production chain.

A research project termed **KabMon** focusing on monitoring of the usage of antimicrobials in calf production systems was facilitated by the German Federal Ministry of Food and Agriculture (Bundesministerium für Ernährung und Landwirtschaft, BMEL, 2020). Within the aforementioned project, a categorization scheme for the different production branches of bovine dairy and beef products was developed (Gorisek et al., 2021). The scheme allows for comparisons of antimicrobial usage between farms sharing the same characteristics with respect to the age of cattle on arrival at the farm, duration of the rearing or fattening periods as well as the number of movements of animals within a certain production system. The scheme was established on basis of expert opinion; it categorizes farms based on production

characteristics and illustrates animal movements from one system to another on a timeline reflecting the lifetime of cattle from birth to slaughter (Gorisek et al., 2021). Four major categories (A, B, C, D) were identified with respect to the management of bovine youngstock. Subordinated systems differ from each other by production characteristics (mainly dairy, double-purpose, beef) **(Fig. 1)**.



Preliminary Fig. 1: Categories of dairy and beef producing farms in terms of animal movements and supplier- customer chains as defined in the project KAbMon (Gorisek et al. 2021).

Category A comprises:
1st Dairy farms on which either dairy cows are kept or
2nd Cows of double-purpose breeds
3rd Beef cattle farms.

Farms belonging to **Category A** do not buy any youngstock from other farms on a regular basis.

On the **dairy and double-purpose farms** female calves are raised as replacement heifers and introduced into the herd of dairy cows after calving. Only on a few dairy farms (mainly those keeping double-purpose breeds) male calves do not leave the farms and are kept for beef production until slaughter. A clear epidemiological link exists between herd mates and between mothers and offspring on the latter's farms.

Few dairy farms assign the task of rearing replacement heifers to specialized farms and receive pregnant heifers at request. **Rearing farms** for dairy heifers mostly have

contracts with only one farm or a small number of farms of origin. In case of such rearing farms, a clear epidemiological relationship exists between the farms of origin and the receiving rearing farm.

Most dairy farmers sell male calves at a young age to specialized producers. These belong either to the veal calf sector, or to operations specialized in fattening of bulls predominantly in intensively run indoor systems which are assigned to one of the other categories.

On beef cattle farms the animals are reared for meat production either outdoor on extensive grass-based systems, or indoors on intensive indoor systems. If the animals stay with their mothers or within the same farm they can be assigned to the same epidemiological unit. Calves born in a beef herd are either sold at an early age or kept with their dams as sucklers until weaning at an age of several months. Subsequently these animals are sold to specialized producers that are assigned to one of the other categories.

Category B
Farms assigned to **Category B** receive calves younger than 10 weeks of age (termed starters). Subordinated groups of farms that fall within this category differ in the duration of the stay of the animals on the farm until these are sold or slaughtered.

Category B comprises:
1st Veal calf producers (white, rosé)
2nd Farms specialized in rearing calves up to weaning

Veal calf producers either producing white, or red veal. Most of the European veal production is in North-western Germany, the Netherlands, Belgium, and France while the overseas veal production mainly takes place in Canada.

The term veal in this context is reserved for calves younger than 8 months. Depending on the rearing conditions veal calf industry differentiates between white veal and rosé veal. Calves are collected by salesmen from their farms either at an age of approximately two weeks and older or following weaning (rosé veal). Generally, the animals pass through a livestock collecting center before entering the veal farm. Veal farms maintain an all-in-all-out policy.

Some veal calf producers routinely receive calves from a small number of farms of origin on a contractually agreed basis. Under these preconditions, an epidemiological link can be drawn between the farms of origin and the receiving farms.

Specialized rearing farms (Fresseraufzucht in German) raise calves from a very

young age (< 10 weeks) until they are sold to specialized beef producers post weaning (e.g. fattening bulls in intense indoor systems).

Farms assigned to **Category C** receive calves just after weaning at an age > 10 weeks (ruminating cattle termed Fresser in German) from specialized farms belonging to **Category B** (rosé veal producers, fattening bull producers) or fatten beef cattle originating from **Category A** farms following separation from their mother at several months of age. Whenever only a small number of the same farms of origin deliver cattle to the receiving farm on a contractual basis, an epidemiological link is given.

Category D comprises collecting centeres and stables of cattle traders.

As described above some receiving farms of **Category B and C** maintain fixed supplier – customer relationships, buying animals from a limited number of farms of origin. In addition, to improve the health status of their animals, arrangements are met with respect to the health status of the animals of origin either requiring seronegativity, or freedom of disease (for example *Mycoplasma bovis*), or immunization against specific pathogens already on the farm of origin. Under such circumstances and whenever suppliers and customers work on basis of long-term contractual agreements with a limited number of farms of animal origin an epidemiological link is given. This applies especially when vaccination strategies based on routine diagnostic sampling are already implemented on the farms of animal origin, or disease outbreaks can be traced back by diagnostic sampling to the farm of origin.

3.3.3 Preconditioning of calves to reduce crowding associated disorders

Immunologic preparation of calves facing uncertain futures at unknown destinations is an economic and technologic dilemma involving professional, ethical, and scientific considerations (Kahrs, 1985). Most antibiotics are administered to groups of youngstock that originate from various farms following transportation and arrival on the receiving farm.

Immunization of calves at arrival at the receiving farm is essential but is regarded as second choice option due to lack of efficiency (O'Connor et al., 2019). To this end, todays' strategies of future-oriented veal and beef producers include fixed seller-buyer relationships such that animals are bought from a limited number of known farms of origin that provide preconditioning immunization before transportation. The latter strategy may increase the likelihood of healthy arrival and acclimatization phase. Vaccine decisions for preconditioning programs shall protect the calf from discomfort or death from specific infections and their consequences and increase profits of the farmers (Kahrs, 1985). Preconditioning of calves was shown to result in improved health, weight gain, feed efficiency, and animal welfare in US feedlot and has gained

more and more followers (Hilton, 2015).

3.3.4 Use of autogenous vaccines in bovine health management

In cattle, autogenous vaccines have not as widely been used in preventive health programs as in pigs and poultry. They fill a gap when new agents emerge for which no vaccines are available, or when commercial vaccines have been proven ineffective or not available on the market (Chase, 2004). A selection of pathogens that have been incorporated in autogenous vaccines for cattle includes: *Escherichia coli* for prevention of neonatal diarrhea, and neonatal septicemia*, Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* for prevention of Bovine Respiratory Disease (BRD)*, Moraxella bovis, Moraxella bovoculi* and *Mycoplasma bovoculi* for prevention of Infectious Bovine Keratokonjunctivitis (IBK), *Clostridium perfringens* for prevention of abomasitis, enteritis and enterotoxemia*, Salmonella* Dublin and *Salmonella* Typhimurium for prevention of Salmonellosis*, Papillomavirus* for treatment and prevention of papillomatosis and various bacteria species for prevention of mastitis and infectious claw disorders.

3.3.4.1 Bovine Respiratory Disease (BRD)

The term Bovine Respiratory Disease (BRD) describes the “clinical appearance of a disease of the respiratory tract” in youngstock and adult cattle. It comprises various disorders of the respiratory tract with Enzootic Bronchopneumonia (EB) of youngstock being the most important one because of its impact on animal welfare and its enormous economic losses due to treatment costs, loss of animals, reduced weight gains, minor carcass quality, and extra labour (Peel, 2021; Fulton, 2009). Two different forms of Enzootic Bronchopneumonia are differentiated: a seasonal form preferentially occurring in late autumn (October, November) and in spring (March, April) and a non-seasonal form also termed “crowding associated BRD” that occurs independently of the season. While the seasonal form of Enzootic Bronchopneumonia preferentially affects rearing calves on dairy farms, the non-seasonal form is observed on farms that receive youngstock from different farms of origin. A great spectrum of different viruses is isolated from cases of EB among these Bovine Viral Diarrhea Virus, Parainfluenza Virus type 3, Bovine Respiratory Syncytial Virus, Bovine Herpes Virus type 1, Influenza D virus, coronaviruses and adenoviruses (Smith 2021). In addition, multiple bacteria species, predominantly *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, Trueperella pyogenes* and *Mycoplasma spp.* are cultured from material obtained from animals with EB (Fulton, 2009). The term “Shipping Fever” is a manifestation of the crowding disease but is characterized by severe systemic clinical disease characterized by septicemia and bronchopneumonia. While *Mannheimia haemolytica* is consistently cultured from diseased animals, other agents of the BRD-complex are inconsistently isolated (Rehmtulla and Thomson, 1981). BRD is

multifactorial by origin. Recent evidence demonstrates the role of the nasopharyngeal microbiome in the pathogenesis of EB (Timsit et al., 2016). In outbreaks of EB pathogenic bacteria species were shown to overgrow the commensal microbes.

Evidence for efficiency of commercial vaccines is demonstrated in challenge experiments or field studies. Various meta-analyses however, demonstrate substantial weaknesses in field trials due to missing controls or comparisons with historic controls (Richeson and Faulkner 2020). Due to limited applications of autogenous vaccines, data on efficacy and safety of these vaccines are only sparse. The results of a network meta-analysis however, suggest that there is insufficient evidence to support the proposition that various commercial vaccines and one autogenous vaccine are effective at preventing outbreaks of BRD among beef cattle when administered at feedlot arrival (O'Connor et al., 2019). The latter findings might be related to insufficient immune responses following transportation and crowding and plead to vaccinate calves already on the farm of origin.

3.3.4.2 Mycoplasma bovis in Bovine Respiratory Disease

Mycoplasma bovis is a pathogen with world-wide distribution that can cause various clinical disorders including bronchopneumonia, otitis, encephalitis, arthritis and tendosynovitis in veal calves, beef calves and feedlot cattle (Caswell et al., 2010; Caswell and Archambault, 2008; Nicholas et al. 2008). *Mycoplasma bovi*s is transmitted via direct contact or via milk of infected cows. Its role as primary pathogen is still under discussion as it can be cultured from the respiratory tract of healthy calves (Perez-Casal, 2020). *Mycoplasma bovis* is considered a secondary pathogen in the Bovine Respiratory Disease complex that acts in concert with other pathogenic microorganisms causing a severe therapy-resistant caseonecrotic bronchopneumonia (Panciera and Confer 2010; Nicholas et al. 2008). In addition, systemic spread of *Mycoplasma bovis* can lead to serofibrinous arthritis and Otitis media. Treatment failures and chronicity of disease are a consequence of the ability of *Mycoplasma bovis* to evade the immune defence mechanisms of its host for example the expression of variable surface proteins and biofilm formation (Perez-Casal, 2020). For this reason, attention has been drawn to vaccines as a more sustainable and cost-efficient solution (Dudek et al., 2021). At present, there is no commercial vaccine marketed in countries belonging to the European Union.

Recently, a vaccine from the USA was introduced in the UK (Dudek et al., 2021). In several studies, the efficacy of autogenous vaccines prepared with different inactivates and adjuvants as well as experimental vaccines were tested with variable results (Nicholas et al., 2019; Dudek et al. 2021). The use of autogenous vaccines in three different trials including controls on veal calf farms and beef producing farms resulted in lower mortalities, higher weight gains and a lower percentage of calves with severe

lung lesions and pleuritis compared to controls (Nicholas et al., 2019). Some experimental vaccines caused granulomas at the injection site or even exacerbation of the disease (Dudek et al., 2021; Nicholas et al, 2019).

3.3.4.3 Infectious Bovine Keratoconjunctivitis (IBK)

The term Infectious Bovine Keratoconjunctivitis (IBK) is defined as a herd disease of cattle with high morbidity (>2% in calves and >0.6% in adult cows) and rapid spread. Clinical symptoms are restricted to the eye, including conjunctivitis and/or keratitis with a significant number developing corneal ulcerations (> 10% of affected or more) (Kneipp 2021). Diseases of individual animals suffering from keratoconjunctivitis do not fall under the latter definition if the herd remains unaffected. IBK is a disorder multifactorial by origin that is affecting the eyes and that is characterized by profuse lacrimation in the initial phase, blepharospasm, serous to mucopurulent ocular discharge, conjunctivitis and keratitis up to ulceration and rupture (Kneipp 2021; Schnee et al., 2015). Multiple factors have been shown to contribute to the occurrence of IBK: 1st microorganisms, 2nd environmental conditions, 3rd trauma. Various bacteria species have been isolated from clinical cases during herd outbreaks of IBK among these *Moraxella bovis* and *Moraxella bovoculi* (Schnee et al., 2015). A prerequisite for pathogenicity of *Moraxella* spp. is ability to adhere to the cornea which is mediated by pili. Researchers were able to reproduce IBK in a bovine model by scarification of the cornea and subsequent infection with *M. bovis*, but not *M. bovoculi* (Angelos et al., 2021). As the latter bacterial species are also isolated from apparently healthy animals and recombination between different Moraxellaceae has been reported, their exact role in the complex of IBK is not completely understood. In addition, *Mycoplasma bovis*, Bovine Herpesvirus-1, chlamydia, listeria, and adenovirus but not *Moraxella spp.* were isolated from field cases of IBK (Kneipp, 2021; Schnee et al., 2015). Determining the etiology of individual outbreaks is challenging as the isolation of an agent after the appearance of clinical symptoms does not establish causation (Loy et al, 2021). To this end, diagnostic sampling and isolation of pathogens during field outbreaks deserves special attention.

The first line defence mechanisms of the bovine eye include the tear film and the conjunctival-associated lymphoid tissue (CALT). Vaccines should activate the ocular defence mechanisms without causing an excessive immune response that could damage the eye or the animal. Various studies including parenteral administration of viable, heat-killed, or formalin-killed *Moraxella bovis* were shown to generate an immune response (Angelos et al., 2021). In some animals, viable *Moraxellas bovis* vaccines caused anaphylactic reactions. In animal models, administration of whole *Moraxella bovis* cell-derived vaccines resulted in protection against IBK and induction of IgG as well as IgA antibodies. In the USA, three types of vaccines against IBK are commercially available: licensed vaccines, conditionally licensed vaccines and

autogenous vaccines. Although experimental studies on different vaccines for prevention of IBK delivered encouraging results, up until now there is no evidence that commercially available or autogenous vaccines are effective in the field (Maier et al., 2021; Funk et al., 2009). The authors encourage veterinarians who use vaccines to carefully evaluate the results following vaccinations against IBK in the field.

3.3.4.4 Abomasitis and enteritis caused by Clostridium perfringens

Clostridial abomasitis and enteritis in the bovine species (also termed enterotoxemia) are common disorders of ruminants characterized by necrosis of the abomasal and intestinal mucosa and sporadically nervous symptoms (Bus et al., 2019; Simpson et al., 2018; Goossens et al., 2017). These disorders are caused by exotoxins produced by *Clostridium perfringens* within the lumen of the gastrointestinal tract of cattle (Simpson et al., 2018). Clinical disease is associated with rapid bacterial overgrowth within the gastrointestinal tract and subsequent release of exotoxins. Due to its sudden onset and rapid disease progression, affected animals are frequently found dead or in agony. Although the clinical disease was reproduced in a bovine ligated intestinal loop model, pathogenesis of the various disorders caused by *Clostridium perfringens* is still not fully understood (Uzal et al., 2018; Goossens et al., 2017; Uzal et al. 2015; Valgaeren et al., 2013). Three key components, however, were identified as predisposing factors: 1st The presence of *Clostridium perfringens* in the gastrointestinal tract, 2nd a high level of protein and carbohydrates in the feed, 3rd decreased intestinal motility (Simpson et al., 2018). The Haemorrhagic Bowel Syndrome (HBS) forms a distinct disease entity most often affecting adult cattle. The disorder is multifactorial by origin and characterised by haemorrhages into the intestinal lumen of segments of the jejunum leading to its obstruction. In fatal cases intestinal perforation may occur. *Clostridium perfringens* and *Aspergillus fumigatus* have been shown to be involved in HBS.

Clostridium perfringens is a gram-positive, anaerobe spore forming microorganism that is present in the environment and in the gastrointestinal tract of cattle. Pathogenicity of *Clostridium perfringens* originates from its ability to produce exotoxins because of cumulative effects of risks. Based on the capacity to form toxins (alpha (CPA), beta (CPB), epsilon (ETX), iota (ITX), enterotoxin (CPE), necrotic enteritis beta-like toxin (NetB), seven genotypes of *Clostridium perfringens* (A-G) are differentiated (Zaragoza et al., 2019). No individual strain, however, produces all toxins and diseases are usually caused by a combination of different toxins. An overview over the different diseases caused by the different subtypes of *Clostridium perfringens* in ruminants is provided by Simpson et al. (2018).

Diagnostic testing including genotyping should be performed on material collected ante-mortem, or immediately post-mortem from the abomasum or intestinal tract of

cattle. In addition, necropsy and histological examination of freshly dead animals are of value. Demonstration of clostridial toxins by mouse-neutralization test or enzyme-linked immunosorbent assay are not commonly available (Simpson et al., 2018).

Vaccination is considered a cornerstone in the prevention of clostridial disease in ruminants. The vaccines are reviewed by Zaragoza et al. (2019) and Simpson et al. (2018). The aforementioned authors provide a list of recommendations based on animal species, age and including timing and frequency of vaccinations for the different production systems. Commercial clostridial vaccines are usually combination vaccines against several clostridial species, often including bacterin-toxoids produced by different *Clostridium* species (Ständige Impfkommission Veterinärmedizin, 2021; Zaragoza et al., 2019).

Animal types B, C, D outbreaks in pigs and ruminants have been proven to be effectively prevented by vaccination with crude toxins or bacterin-toxoid vaccines (Zaragoza et al., 2019). However, there are no commercial vaccines available that confer protection against the whole spectrum of toxins produced by *Clostridium perfringens*. Autogenous *Clostridium perfringens* vaccines can also be used under the given restrictions when commercially available vaccines have been ineffective or are unavailable. Formalin-inactivation, however, could lead to reduced immunogenicity of bacterin-toxoid. As long as the pathogenesis of diseases in cattle caused by *Clostridium perfringens* is not completely understood, veterinarians have to rely on the existing spectrum of vaccines.

3.3.4.5 Infections caused by Salmonella

Salmonella is a genus of gram-negative, facultative anaerobic bacteria that belong to the family *Enterobacteriaceae*. There are two recognized species within the genus: *Salmonella enterica* subspecies *enterica* and *Salmonella bongori* (Holschbach and Peek, 2018). *Salmonella* are delineated by their serovar/serogroup classification *Salmonella enterica* subspecies *enterica* serovar Typhimurium or *Salmonella* Typhimurium in brief. *Salmonella* Typhimurium and *Salmonella* Dublin are serovars of clinical importance in cattle causing septicaemia, enterocolitis, and abortions. In contrast to most *Salmonella* serovars that are non-host adapted, *Salmonella* Dublin is the host-adapted serovar of cattle. Besides the disorders given above, *Salmonella* Dublin was shown to cause pneumonia in cattle (Holschbach and Peek, 2018). Young calves are especially susceptible to diseases caused by *Salmonella*. In the Netherlands. 8-9% of dairy herds are infected with *Salmonella* and about 1% experience a clinical outbreak each year (van Schaik et al., 2007). In 2020, *Salmonella* Typhimurium was isolated from 37% of the outbreaks in German cattle herds and *Salmonella* Dublin from 32% (Methner, 2021). Not all cattle infected by *Salmonella* develop clinical symptoms. Some of the aforementioned animals and those that

recover from clinical disease change to a carrier status with intermittent shedding of the pathogen posing a risk for the entire herd (Foster et al., 2021). Although there are various routes of infection the faecal-oral route is the most important one. *Salmonella* can be introduced onto a farm by purchase of animals, by feedstuff, water, rodents, birds, and visitors. Salmonellosis in cattle is an animal welfare issue causing substantial economic losses. The importance of *Salmonella* in cattle, however, originates from their zoonotic potential. In addition, increased frequencies of antimicrobial resistant *Salmonella* isolated from humans and the presence of *Salmonella* in meat from cattle, causes concerns in consumers about the usage of antimicrobials in food animals (Horton et al., 2020; Alexander et al., 2008). Various control programs were established in the member states of the European Union (Santman-Berends et al., 2021; Holschbach and Peek, 2018). In Germany, Salmonellosis in cattle is a notifiable disease. Prevention includes biosecurity measures including pest control, bacteriological examination of faeces or tissues obtained from diseased animals, isolation of diseased animals and culling of shedders. Control and eradication programs rely on surveillance by bacteriological examination of faecal or environmental samples in regular intervals, and/or detection of antibodies in blood or bulk milk samples (Santman-Berends et al., 2021).

In the USA and Germany parenteral, intranasal, or oral administration of commercially available vaccines or autogenous vaccines against *Salmonella* Typhimurium and *Salmonella* Dublin are recommended to alleviate the severity of clinical symptoms and reduce shedding of *Salmonella* (Holschbach and Peek, 2018; Rheinland-Pfalz, 2017). Following the use of commercial or autogenous vaccines in challenge studies and field trials in US-feedlots, no or reduced numbers of *Salmonella* were recovered from peripheral lymph nodes of vaccinated cattle in contrast to controls and no pathogens were recovered from control cattle housed adjacent to the vaccinated animals (Horton et al., 2021; Edrington et al., 2020). Vaccination however, interferes with *Salmonella* control programs with standard bacteriological and serological detection methods (Holschbach and Peek, 2018).

3.3.4.6 Mastitis

Despite intensive advisory and research activities bovine mastitis still belongs to the most challenging disorders on dairy farms causing animal suffering, and economical losses due to treatment costs, discarded milk, extra work, and unintentional culling. The dry period and the early period following calving, form the most vulnerable periods with respect to intra mammary infections (Ruegg, 2012; Bradley et al., 2015). Substantial amounts of antibiotics are used for dry cow therapy and for treatments of clinical mastitis cases. As farmers pay particular attention to provide the market with milk as a product of high quality from healthy cows that is free from residues, preventive measures instead of therapy become increasingly important. The spectrum of mastitis

causing agents has shifted in recent years from contagious to environmental pathogens. Contagious mastitis pathogens are transmitted from one cow to the other, either by the milking machine, the hands of the milkers, milk contaminated fomites, or the towels used to clean the teats (Tiwari et al., 2013). The most important contagious agents are *Staphylococcus aureus*, *Streptococcus agalactiae* and *Mycoplasma* species (Tiwari et al., 2013). The term "environmental pathogen" refers to opportunistic bacteria in the environment of the cows which cause mastitis (Ruegg, 2012). The latter group includes gram-negative (among these *Escherichia coli, Klebsiella spp.)* and gram-positive bacteria (among these *Streptococcus uberis* and *Streptococcus dysgalactiae*). In addition, coagulase negative staphylococci (CNS) form a serious threat to udder health (Pyörälä and Taponen, 2009).

Mycoplasma mastitis affects cattle around the world. *Mycoplasma species* are categorized as contagious mastitis pathogens that form a growing problem on large dairy herds (Fox, 2012). The most important species with respect to mastitis are *Mycoplasma bovis, Mycoplasma californicum* and *Mycoplasma bovigenitalium. Mycoplasma spp.* lack a cell wall and use various strategies to overcome the defence mechanisms of their hosts including adherence to cell walls, internalization into cells, immunomodulation, and the ability to colonize host tissues without causing substantial disease. Variable surface proteins (VSP) are a strategy of *Mycoplasma spp.* to evade the host's immune defence. *Mycoplasma* spread from carrier animals that are clinically inapparent to other animals by equipment, milkers' hands, fomites etc. In addition, *Mycoplasma* can spread from one body site to other ones and cause synovitis, arthritis, and pneumonia. Various clones have been shown to circulate in a herd (Fox, 2012). Clinical cases of *Mycoplasma* mastitis are mostly non-responsive to antibiotics and non-steroidal-anti-inflammatory drugs (Nicholas et al., 2008). Severe outbreaks of clinical mastitis were shown to be driven by a single clone (Fox, 2012). A control program includes frequent sampling and diagnostics and consideration of culling of positive cows (GD voor Dieren, 2015).

An investigation of the dynamics of intramammary infections during the dry period on European dairy farms underlines the importance of the dry period and herd-specific characteristics in the pathogenesis of intra-mammary infections requiring tailored advice (Bradley et al., 2015). An effective mastitis prevention program includes optimum housing conditions, adequate nutrition, proper milking procedures and maintenance of the milking equipment, early and adequate diagnosis and treatment of clinical cases, selective dry cow management, and record keeping with evaluations of the program in intervals (Zigo et al., 2021). In addition, hygiene management as well as careful animal handling by skilled staff members are a prerequisite (Tiwari et al., 2013; Ruegg, 2012). As the use of antimicrobials in food-producing animals more and more becomes an issue of the public debate, vaccination gains increasing interest as one tool of a comprehensive mastitis prevention program (Erskine, 2012).

There is a long history of the use of vaccines to combat mastitis pathogens (Mellenberger 1977). The aim of vaccination is to elicit a specific immune response in the vaccinated animal to prevent intramammary infections and the spread of pathogens in the herd (Sordillo, 2018). In addition, vaccination alleviates the severity of clinical disease and reduces economic losses (Sordillo, 2018). The heterogeneity of mastitis pathogens, however, and their spectrum of mechanisms to evade the host's immune defence form significant obstacles of vaccine development (Erskine, 2012).

Most activities in vaccine development for mastitis prevention, however, are still in the experimental phase and only few vaccines against mastitis pathogens are commercially available (Scali et al., 2015; Erskine, 2012; Pereira et al., 2011). In addition, only few controlled trials have been published up to now. In addition, differences between efficacy in challenge studies and field trials were observed. Taken together, most studies demonstrate a clear reduction in the severity of clinical cases and economic advantages following vaccinations, but no differences in the number of intramammary infections compared to controls. In the EU there are commercial mastitis vaccines available for *Staphylococcus aureus*, *Escherichia coli.* Recently, a vaccine against *Mycoplasma bovis* imported from the USA became available in the UK (Nickerson, 2019). In the USA 2.4-50.8% of the dairy herds vaccinate against *Escherichia coli*, 1.5-1.9% against *Staphylococcus aureus,* 0-0.3% against *Mycoplasma,* either with commercially available or autogenous vaccines. Nowadays, innovative technologies of molecular biology allow detection of virulence factors and have the potential to improve udder health by vaccination. The results of a systematic review suggest that vaccines that employ new technologies (DNA and/or recombinant protein vaccines) and innovative adjuvants and some long-standing bacterins achieved good results supporting their role in the prevention of bovine mastitis caused by *Staphylococcus aureus* (Pereira et al., 2010).

Based on the results of a field trial with a herd-specific vaccine in heifers, Tenhagen et al. (2001) concluded that the use of the autogenous vaccine with respect to prevalence of intramammary infections with *Staph. aureus* and incidence of clinical mastitis did not prove efficacy. In US dairy farms autogenous *Staphylococcus aureus* vaccines were shown to reduce the numbers of subclinical and clinical mastitis cases in the field (Nickerson, 2019). In another study on the effect of an auto-vaccine on selected properties of *Staph. aureus,* the authors observed changes in phenotypical properties during the period the vaccine was being used (Nawrotek et al., 2012).

Following the latter authors this phenomenon might explain the lack in efficiency of commercial and autogenous vaccines. They point out the necessity of frequent sampling for diagnostic reasons when vaccinating against mastitis pathogens. With respect to gram-negative pathogens there are core-antigen bacterins and autogenous vaccines used. Most extensively studied commercial vaccines are formulated with the

mutant strain *E. coli* O111:B4 also termed J5 vaccine. Results of vaccination studies are controversial. While three immunizations in the dry period had a 5-fold decrease in the rate of clinical coliform mastitis compared to untreated controls, a field trial using the J5 vaccine did not reduce rate of intra-mammary infections (Erskine 2012). Due to variable results of vaccination trials, the use of vaccines in mastitis control program is still under discussion. Sordillo (2018) assumes that the most practical use of vaccines in mastitis control will be on conjunction with other control strategies.

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3.4 Autogenous Vaccines for Sheep and Goats

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In most European Countries within the EU (excluding GB), sheep and goat industry is very traditional with small farms of mostly less than 50 ewes. Often these small farms are run as a hobby as part time or self-subsistence for the family. The next category of farms are semi-intensive commercial flocks, run in most cases full time. Larger flocks are few and increase to some thousand head. But even in the large sheep and goat farms, the animals are kept traditionally in smaller subunits, with one shepherd running one flock of 300 to 700 adult sheep, with or without their lambs. A horizontal or vertical integration is extremely rare. Most of these farms depend on subsidies. Recent modifications of the Common Agricultural Policy (CAP) of the EU include changes to the conditions for the granting of subsidies, which are now also based on environmental issues and landscape maintenance (Rodríguez-Serrano et al. 2016). Due to the shortage of subsidies and the additional requirements, the number of sheep in most of the 27 EU member states have been in continuous decline during the last two decades. The weaknesses perceived to include the heterogeneity of farms, low productivity, exposure to high production costs, a low technical level of production, a lack of coordination between the different parts of the supply chain, a lack of generational replacement, great dependence on the weather, rising costs, and the lack of medium-term prospects (Rodríguez-Serrano et al. 2016).

In some countries dairy goat milk production shows another trend with increasing numbers of dairy goats, intensification of production, and increasing size of the herds. This development is mainly driven by an increasing market for dairy goat products, specialized dairies, and the possibility to milk goats over several years without kidding. Most of the conventional dairy goat farms keep their goats indoor all year. Organic farms have the obligations to offer their animals runs and access to pasture, but also in the organic sector there is an increase in farm size, intensification and production.

From an epidemiological point of view most sheep and goat flocks can be regarded as closed units. The majority of farms only purchase breeding sires, followed by some farms who buy a limited number of breeding females. The purchased animals are usually introduced into the flock without quarantine. Therefore, vaccination programs focus exclusively on single flocks as the epidemiological unit. In these closed flocks use of autogenous vaccines makes sense to protect or fight against a number of enzootic diseases, where no commercial vaccine for sheep or goats is licensed within Europe, or vaccines licensed for other species, e.g. cattle, can not be rededicated.

In some specialist milk-lamb rearing farms, there is close cooperation with dairy units supplying milk sometimes across borders. Dairy farms and fattening farms are then an epidemiological unit. For these fattening units receiving young lambs at an age of about 2 weeks from different sources, health problems, especially diseases of the respiratory complex, and coccidiosis are common. These milk lambs are often slaughtered with a carcass weight of about 7 to 10 kg, which they reach at an age of 53 to 70 days (Manfredini et al. 1988). This short life span makes it difficult to introduce an active vaccination of the kids or lambs, so that protection of infectious diseases should also be based upon passive immunisation via colostrum. If there are long lasting contracts between the lamb producers and the fattening farms, the implementation of vaccination programs beginning with the vaccination of the ewes before lambing is necessary to improve colostrum quality and transfer passive immunity to the lambs, to protect them from diseases in the first days of their life. Some of these lambs are raised fully artificially with artificial colostrum and milk replacer within their first days of life. Even this approach to preventive measures is a dead-end in these animals and farms.

There are a very limited number of farms, which have trade relations with each other, with one flock producing lambs, sold after weaning to the other farm with more or better pastures or indoor fattening with concentrates. Generally. there are no long-lasting contracts between these farms, so there are unlikely to be joint health strategies which would include any vaccination programme.

In the Mediterranean, especially in Spain the traditional pastoral sheep husbandry system has shifted toward a more intensive system with large herds and high productivity. These changes and lack of specialized labour in the sheep sector have encouraged farmers to cooperate. This cooperation between farmers has led to a system of intermediary feedlots for fattening units between the breeding flocks, holding the sheep and newly-born lambs, and abattoirs where the lambs are slaughtered. In these feedlots, animals are mixed according to their initial weight and maturity characteristics, which usually results in animals from different farms and different previous management practices being mixed together, which may affect the final characteristics of the produced lamb (Campo et al. 2016). In the feedlots, ovine respiratory complex (ORC) is the main health issue and cause of death in all situations during fattening period, although there are different clinical presentations that exhibit differences about the etiology (Gonzalez et al. 2016).

Implementing a vaccination plan against ORC requires: involvement of all farm staff, all production stages, recording data, a positive cost: benefit analysis and continuous monitoring over time. Licensed vaccines for sheep against infections involved in the ORC are available only against *Mannheimia haemolytica* (MH), *Bibersteinia trehalosi* (BT) and *Pasteurella multocida* (PM). According to the antigens contained in the *M. haemolytica* vaccines, these can be divided into outer membrane protein vaccines,

leucotoxoid vaccines and iron regulated protein vaccines (IROMP). Each serotype of MH or BT presents differences in these three antigens, although in the case of IROMP, there is an effective cross protection among them. In addition, strains of bovine origin do not protect sheep and vice versa. For PM, vaccines containing bacteria grown in iron restricted conditions give better results. The lambs should be vaccinated during the first week of life, followed by a booster dose three weeks apart. The best results are obtained with leucotoxoid vaccines, when the serotype that is present in the farm is included in the vaccine, or with IROMP, which can be applied in any situation (Gonzalez et al. 2019). The decision whether AV are included into the vaccination plan depends on the results of serotyping of the bacteria in the flocks of the association and the availability of licensed vaccines covering the serotypes required.

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3.5 Autogenous Vaccines for Fish

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Aquatic animal production has grown multiple fold in recent years, reaching over 90 million tons of product in 2021 (Fig 1.). The diversity of the aquaculture is the highest of any animal production industries, from producing food fish to breeding ornamental/pet animals, currently encompassing over 500 cultured species and more being added every year (FAO, 2020). Globally, the aquaculture leader is Asia (90% world production, with 60% is based in China). Aquaculture industry in the EU is oriented on fewer species with focus on marine fish aquaculture (Atlantic salmon, sea bass, and sea bream), and has ~2% of global production share. European aquaculture is highly regulated sector in the areas of environmental protection. Regulations also apply regarding to health and biosecurity, with note that access to medicines, including vaccines and autogenous vaccines specifically intended or approved for use in designated species is severely limited (Doherty et al, 2019).

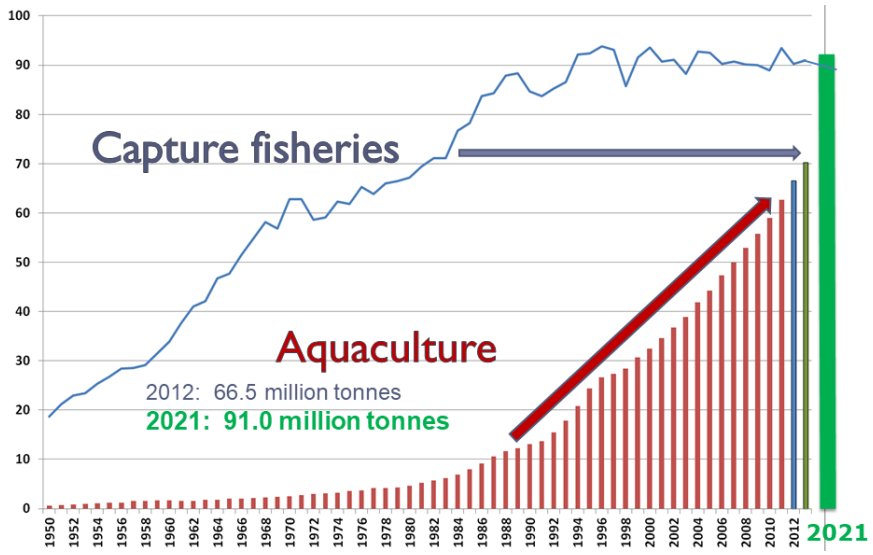

Figure 1. Annual global production of aquaculture and capture fisheries 1950-2021 (in million tonnes)

Specifics of aquaculture production systems are variable and complex. The majority of aquatic animals are produced in open surface waters using cages, ponds, or raceways, and involving indoors production in parts of the life cycles (mostly hatcheries). The ownership structure of aquaculture businesses ranges from individual small-scale producers, to large multinational corporations with elaborate production chains and “in-house” vertical integration from selection and broodstock to final products ready for retail sales. With such diversity of production systems and business interests, combined with regulatory limitations regarding veterinary medical products, it is

exceedingly difficult to address prevention and control of infectious diseases in aquacultured food fish.

In an attempt to standardize aquatic animal disease prevention and control terminology, the OIE (World Organization for Animal Health) Aquatic Animal Health Code and Manual (OIE, 2021) introduced number of definitions that will be used to describe specific conditions of various epidemiological aspects in aquaculture establishments, also as pertaining to autogenous vaccines. Most important definitions for our purpose are:

An *Aquaculture Establishment* is an establishment (e.g. farm) in which amphibians, fish, molluscs or crustaceans for breeding, stocking or sale are raised or kept.

An *Epidemiological Unit*, is a group of animals that share approximately the same risk of exposure to a pathogenic agent with a defined location. This may be because they share a common aquatic environment (e.g. fish in a pond, caged fish in a lake), or because management practices make it likely that a pathogenic agent in one group of animals would quickly spread to other animals (e.g. all the ponds on a farm, all the ponds in a village system).

A *Compartment* is one or more aquaculture establishments (farms) under a common biosecurity management system containing an aquatic animal population with a distinct health status with respect to a specific disease or diseases for which required surveillance and control measures are applied and basic biosecurity conditions are met for the purpose of international trade. Such compartments must be clearly documented by the Competent Authority(ies).

A *Zone* is a portion of one or more countries comprising of: an entire water catchment from the source of a waterway to the estuary or lake, or; more than one water catchment, or; part of a water catchment from the source of a waterway to a barrier that prevents the introduction of a specific disease or diseases, or part of coastal area with a precise geographical delimitation, or an estuary with a precise geographical delimitation, that consists of a contiguous hydrological system with a distinct health status with respect to a specific disease or diseases. The zones must be clearly documented (e.g. by a map or other precise locators such as GPS co-ordinates) by the Competent Authority(ies).

An epidemiological unit (EpiUnit) can be small (an individual farm or “establishment”, or parts of a farm), or large (several farms, a state or province, watershed, or a whole country). Any geographic area that somehow separates one group of animals from another can be the EpiUnit, *provided* that all animals in each unit are managed in a similar way. The separation can be a physical barrier, or simply separated by distance – but the animal population in each unit *must not co-mingle* with animals outside the

unit.

More broadly, the EU regulations mention “epidemiological unit“ as group of animals with “the same likelihood of exposure to a disease agent“ (EU-Regulation 2016/429, Article 4 No. 39) and “animals in units having a confirmed epidemiological link“ (EU-Regulation 2019/6, Article 2 (3). The specifics of aquatic animal production was recently recognized (Grein et al, in press). Here, two most relevant characteristics of aquaculture production sites are mentioned as: 1) “for the special situation of the aquaculture, it should be highlighted that pathogens can move freely into the environment. Animals can therefore be in contact with pathogens without being moved between sites”; and 2)” …for aquatic animals, an epidemiological link also exists between different farms/sites within one geographic area; where an identical pathogen is circulating and spread e.g. by wild aquatic species.”

The OIE clearly expands the concepts of epidemiological units to larger geographic units, allowing for different interpretations of the existing regulations. From this perspective, although this section is focused on application and use of autogenous vaccines in aquaculture establishments, it is very important to emphasize that aquatic animals sharing the same watershed connection are in higher risk of being exposed to the same pathological agent, when compared to terrestrial animal production in the same geographical area. Therefore, autogenous vaccines production, approval and application regulations should recognize these specifics in order to provide maximum safety and efficacy of autogenous vaccines as disease prevention and control tool within larger areas such as compartments and zones (Scarfe and Palić 2020).

Development of fish vaccines and vaccination strategies has rapidly changed the aqua-scape of antibiotic use in a fast-growing industry. Norway’s example success story in the 1990’s demonstrated that use of antibiotics treatments in salmon industry can be reduced to minimum with vaccination programs and improvements in biosecurity practices (NVI, 2016). However, the current situation regarding veterinary medical products, including biologicals and biocides specifically approved for use in aquaculture of food fish, is severely limiting access to legal options used by veterinarians during treatment and control of infectious aquatic animal diseases (Doherty et al, 2019). The recent EU regulation 2019/6 and new animal health laws derived from this directive have since been supplemented with various addendums to address some of the problems that have been identified, including more uniform standards for autogenous vaccine production and use in food fish aquaculture.

So far, autogenous vaccines in finfish aquaculture have been used with variable success. Inherent issues such as pathogen variability, different field conditions, and vaccine application techniques have contributed to such variability. Furthermore, standardization of production process quality control and assurance has been

generally missing across EU member states. The EMAV is spearheading efforts for setting industry standards for autogenous vaccine production, and it is expected that regulatory agencies will recognize benefits of safe and efficient aquaculture autogenous vaccines, which are much desired addition to aquatic veterinarian toolbox.

The diversity of aquaculture production systems, species, and enterprise sizes are effectively preventing descriptions and discussions of every specific situation, especially within limitations of the first edition of this manual. Therefore, it is currently only possible to focus on common approaches using epidemiological unit (EpiUnit) approach and discuss basic principles of aquatic animal infectious disease control and prevention with application of autogenous vaccines as part of a comprehensive EpiUnit biosecurity program. It is expected, however, that specific case studies will be made available as examples of autogenous vaccines utility in future editions of this Manual. It is suggested that following steps are taken into account when discussing possible use of autogenous vaccines in aquatic animal disease control and prevention:

Assessment of existing and potential hazards and risks associated with the *specific* EpiUnit. In order to determine what diseases might be hazards, and severely affect the EpiUnit, it is suggested to use semi-quantitative (weighted) approach* to estimate the risks and impacts of each disease and prioritize the diseases for inclusion in the vaccination program. Using cumulative scores (sum of risk and impact scores) the first step would be to select the highest-ranking diseases to include as candidates for autogenous vaccine development for the specific EpiUnit (Figure 2).

		Consequences				
		Insignificant	**Minor**	**Moderate**	**Major**	**Severe**
Likelihood	**Almost Certain**	Medium	High	High	Extreme	Extreme
	Likely	Medium	Medium	High	Extreme	Extreme
	Possible	Low	Medium	Medium	High	Extreme
	Unlikely	Low	Low	Medium	High	High
	Rare	Low	Low	Low	Medium	High

Figure 2. A generic qualitative risk-consequences chart useful for estimating the impact of a disease on an EpiUnit. To prioritize diseases considered to be hazards to the EpiUnit, the semi-quantitative impact (I) can be calculated by assigning a value (1-10) to each consequence (C) and likelihood (L) and used in a formula [I = C x L] to establish disease rankings. The highest ranked diseases should then receive the most attention when developing the biosecurity plan for the EpiUnit, particularly when resources are limited. Adapted from (Scarfe and Palić 2020).

* In more complex EpiUnits such as larger farms, compartments, zones, or countries/regions, a more formal risk assessment process is likely needed in order to provide better estimate of priorities and associated actions to be developed for disease control and prevention program (e.g. use of FAO Risk Assessment tool (Bondad-Reantaso et al 2009)).

The expected output from this step is a prioritized list of diseases with past, current or potential serious impact on the farm. i.e. those that severely decrease production, are zoonotic, would cause unacceptable morbidity or mortality, would result in regulatory restrictions, would negatively affect the reputation or economic viability of the farm, or might have serious impacts on wild populations or other farms where the farm is located. The list should not only include those diseases that are reportable to a governmental agency, but should also include diseases the owner feels are important.

Selection of pathogen candidates for autogenous vaccine development in the EpiUnit. The conventional approach for autogenous vaccine production, also most frequently enforced by the regulatory authorities, is to sample and isolate a pathogen from the affected EpiUnit population, then produce it in required quantities and inactivate using approved methodology. Using prioritized disease list for the EpiUnit (farm, establishment, compartment, zone), it is necessary to select a candidate with highest cost-benefit potential for the operation that will at the same time comply with the regulatory requirements of the respective country. In practical terms and most frequently, the pathogen(s) suitable for autogenous vaccine production and application belong to the realm of bacteria, and in rare cases parasites (e.g. *Philasterides dicentrarchi*). Viruses are not routinely considered as candidates for fish autogenous vaccines; however, several manufacturers have produced and applied viral autogenous vaccines in aquaculture.

Species of bacterial pathogens presenting as high concern for aquaculture operations differ to some extent between freshwater and marine ecosystems, as well as between warm and cold-water fish species. Most frequently however, they belong to Gram (-) such as *Aeromonas, Vibrio, Flavobacterium, Yersinia, Pseudomonas, Pasteurella*. Less common are also Gram (+) or acid-fast positive bacteria belonging to *Streptococcus, Renibacterium, Mycobacterium, Nocardia, Clostridium,* etc. It is important to note that many (bacterial) pathogens (and their respective strains/isolates) can be present in fish without clinical symptoms, as well as in surface water sources and wild aquatic animal populations (as hosts or carriers, also including invertebrates, birds etc.). From the autogenous vaccine development and use perspective, this situation may require that epidemiological links between current and potential disease outbreak sites are subjected to thorough analysis, possibly with assistance of Geographical Information System based models.

As most of the aquacultured species (except Atlantic salmon – *Salmo salar*) currently belong to the Minor Use Minor Species category (MUMS), the prophylactic approaches are frequently not a high priority for big companies, considering costs associated with registration of commercial vaccines. On the other hand, while the cost of autogenous vaccines is less prohibitive, the regulatory environment may be overly restrictive in interpretation of “one farm-one pathogen” language in the national legislation. It is

becoming more obvious that epidemiological units in aquaculture may require broader implementation of prophylaxis, based on common antigenic determinations of the strain that is widespread in the corresponding establishment (farm), compartment, or zone (watershed). The analogy may be drawn that if we put out only parts of a forest fire, and leave “hot spots” in the neighbourhood unattended, only because administratively they belong to a different establishment, the fire is likely to come back and spread further. Similarly, if the isolate or strain of the pathogen is common within a watershed with multiple establishments, vaccinating only one (sub) population is less than optimal use of resources, and with doubtful results regarding disease control within the area.

Therefore, the utility of autogenous vaccines in aquaculture is strongly dependent upon the relationship between producer, veterinarian and government. It is strongly correlated with the use of veterinary biosecurity principles, including risk analysis, surveillance, and selection of pathogens suitable for autogenous vaccine application in an epidemiological unit of concern. As part of the overall biosecurity strategy, and with use of current technologies to select best candidates and produce standardized vaccine with reasonable cost, the autogenous vaccines have a potential to become a powerful tool in aquatic animal disease control and prevention, as well as play a significant role in reduction of antibiotics use in aquatic animals.

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3.6 Autogenous Vaccines for Dogs and Cats

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In dogs and cats, the use of autogenous vaccines (AV) is almost entirely focused on therapeutic indications. Due to unsatisfactory therapeutic options, the use of AV for certain indications became established to a certain extent decades ago. However, due to the current objectives of limiting the use of antibiotics, the possibilities of vaccines are coming much more into focus.

Especially in the case of chronic and chronic-recurrent infections, treatment with AV should be considered. Although the concept of AV has been known for a long time, it is not present as a therapeutic alternative to some people (Mac Donald et al., 1972; Mayr et al., 1987).

3.6.1 Mode of action and principle of an AV

An AV serves as an immunostimulatory therapy with activation of the cellular and humoral immune response. When applied locally, e.g. by inhalation for rhinitis, it leads to an increase in the local immune response (Baljer et al., 1990). The AV is produced from the pathogens isolated directly from the disease, and is thus animal- and pathogen-specific. Prior cultivation and identification of the pathogen(s) is therefore necessary before the production of the AV.

After primary cultivation and pathogen identification, the pathogen is multiplied in pure culture and then inactivated. If multiple relevant germ types are isolated from the disease, these can also be combined in an autovaccine, taking into account the pathogenetic evaluation. The use of an AV is particularly indicated in the case of chronic and recurrent illnesses such as pyoderma or chronic recurrent diarrhoea. Especially when there is an antibiotic resistance situation or treatment successes fail to materialise, the AV can be used in an attempt to positively influence the course of the disease.

In the following, our own experiences are evaluated and then data from the international literature are discussed.

3.6.2 Indication and use of autovaccines

In a survey by means of questionnaires (returned 76) on the experience of AV treatment, 51.3% of the practices participating in the survey used AV for chronic recurrent disease and 38.2% for chronic disease. Of the animals, 94.7% were pre-

treated (antibiotics 94%, anti-inflammatories 31%, homeopathics / herbal medicines 28%, other 11%; multiple answers possible).

The most frequent indication for the use of an autovaccine was diarrhoea.

Fig. 1: Frequency of indications in the evaluated autovaccine treatments

3.6.3 Application of the autovaccine

Depending on the indication, the application is carried out by subcutaneous injection and/or oral administration. In the case of an upper respiratory tract infection, inhalative application is also possible.

Oral application can be achieved by inclusion in food and can be carried out at home by the owner. The lack of acceptance of oral application by a cat towards the end of treatment, led to premature discontinuation of oral application in only one case.
AV therapy can also be given during an existing antibiotic treatment. This was done in 28.4% of the evaluated treatments.

3.6.4 Side effects - severity and frequency

The side effects described are a rise in temperature, dullness, local inflammatory reactions up to a short-term worsening of the disease state or shock reactions. These are observed only rarely. In eight of the 76 evaluated AV treatments, corresponding side effects were reported. Due to the side effects that occurred, four practices discontinued the treatment prematurely. In two of these animals, the presence of other underlying diseases was later detected, which hindered the success of the AV treatment.

If mild side effects occur, an attempt can be made to counteract this by reducing the dose.

3.6.5 Prospects for success

According to other studies, which report success rates of 43.7%-80%, 61.3% of the

practices we surveyed were able to report a significant improvement to recovery after AV treatment (Mayr et al., 1987; Klein et al., 1999; DeBoer et al., 1990; Agut et al., 1996). If animals with other underlying diseases are excluded from the calculation, 68.3% of the treated animals showed a significant improvement in symptoms up to recovery.

In patients suffering from pyoderma, 83.3% of the treated animals showed a clear improvement to recovery, which means that the success rate for this frequent indication was above average. If animals with later diagnosed underlying diseases (e.g. fungal infections, allergy) are not included in the calculation, 88.9% of the animals treated with an AV for pyoderma showed good to very good success. Thus, satisfaction with the choice of an AV was also very high for this indication (91.7%). When interpreting these results, it should be noted that these are usually therapeutic successes in chronic and chronic-recurrent, usually already pre-treated disease processes. A direct comparability of the indications is not given due to the different number of evaluated AV treatments.

In each case, 13 patients showed a slight improvement or no changes. In 23.1% of these animals, other underlying diseases impeded the success of the treatment. This shows that a good diagnosis to determine the primary cause is also indispensable before using an AV in order to avoid a failure of the therapy and unnecessary costs for the animal owner.

The recurrence rate was 10.6% (of which 22.2% due to other underlying diseases). To prevent recurrences, repeat vaccination at monthly to six-monthly intervals may be recommended (Mac Donald et al, 1972). As the recurrence rate can be higher, especially in pyoderma, a longer application period is recommended for this indication.

3.6.6 Acceptance by the animal owner

80.3% of the veterinarians interviewed, stated that they were satisfied with the choice of AV therapy in the cases surveyed. The satisfaction of the patient owners was assessed by the treating veterinarians as very good by 26.7% and good by 38.7%. It was estimated by 60.3% of the veterinarians that the choice for AV therapy had contributed to the improvement of the patient-owner-veterinarian relationship. Overall, 94.4% of the surveyed veterinary practices would provide AV treatment again and 86.8% would advise other colleagues to do so.

3.6.7 Autogenous vaccines in the treatment of canine pyoderma

Most literature reports on the use of autogenous vaccines are available on the treatment of canine pyoderma. The pathogen spectrum mainly includes

Staphylococcus (S.) intermedius and *S. pseudintermedius*, these pathogens are usually found in older literature as *S. aureus* (biovars E and F). Wilson et al. (2019) published a retrospective study on the use of vaccines in the treatment of recurrent canine pyoderma. For this, they evaluated the treatment records of 231 vaccine prescriptions and 480 repeat orders over a period of 12.5 years. They evaluated the use of antibiotics for 12 months before and after the start of the vaccinations. As a result, they evaluated AV as a potentially valuable contribution to the therapy of canine pyoderma. These vaccines were prepared according to the method of Curtis et al. (2006). Five older studies (cited by Wilson et al., 2019) had come to similarly positive results. Another publication also reported the positive effect of an AV based on Propionibacterium (now Cutibacterium) acnes (Becker et al., 1989).

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3.7 Autogenous Vaccines for Zoo Animals and Captive Wildlife

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The vaccination and also the medication of zoo animals is a special problem. For very many, if not most species, there are no approved medicines and vaccines available. Remedies are not to be expected, because even for approvals under MUMS conditions, the numbers of individuals are too small in most cases. In addition to the economic problems however, technical difficulties also stand in the way of approval procedures. Safety and efficacy tests on target animals are required in approval procedures, and ideally challenge tests should be carried out on target animals. For many reasons this is not possible for most zoo animal and captive wildlife species. On the other hand, many zoo animals are of great importance for species conservation and represent high ethical and material values.

Thus, rededications of vaccines are at the top of the list where safety considerations naturally play a decisive role. Here, even in related species, significant differences in the tolerability of vaccines can occur. An illustrative example is the tolerability of live distemper vaccines. In domestic dogs, these products have proven themselves for decades and have replaced inactivated vaccines, but in wild canids they are often incompatible. It follows that any re-designation requires a very careful examination of all available data.

For this purpose, internationally recognised information is available, e.g. the European Association of Zoo and Wildlife Veterinarians publishes a Transmissible Disease Handbook (www.eazw.org), the American Association of Zoo Veterinarians (AAZV) edits an Infectious Disease Manual (https://www.aazv.org). In addition, various websites (www.vetspace.2ndchance.info), international standard books (Fowlers's Zoo and Wild Animal Medicine, Vol. 1-8; Miller- Fowler's Zoo and Wild Animal Medicine, Vol.9, 2018) and the conference proceedings of various national and international zoo veterinary associations are important sources of information.

Autovaccines (AVs) are also an instrument for combating infectious diseases in zoo animals. In addition to prophylactic use, the therapeutic use of AVs is also possible for certain indications, for example in papillomatosis. As a rule, each zoo is to be regarded as an epidemiological unit. The exchange of animals plays a major role between zoos as well as private keepers and partly takes place on a global scale.

International breeding programmes run in the interest of species conservation and biodiversity organise an international exchange of breeding animals. Since animals of important species are documented in International Studbooks, the epidemiological

links can be well documented for a necessary use of AVs. Thus, if a zoo A, where an AV is used in a certain animal group, receives a new animal from a zoo B, the AV can be transferred from zoo A to zoo B and used before transportation of the animal. Of course, the relevant transport- and customs regulations of the countries involved must be complied with. If, as in this fictitious example, a zoo uses AV in certain animals, vaccination with the AV is recommended in the case of animals arriving from other holdings. Breeding groups kept in zoos (stock A) are often stable over many years in the same space and can thus develop a microflora typical of the stock, which can pose a greater problem for incoming animals from other stocks (stock B) than for the animals of stock A that have adapted to it.

Examples of AVs used in zoos are listed below, with more detailed information presented in section 2:

- *Yersinia-pseudotuberculosis* vaccines in birds, rodents, ruminants, monkeys
- *Klebsiella* vaccines in monkeys
- Papillomatosis autovaccine in ruminants and elephants
- Sarcoid autovaccines in zebras
- Vaccines against Lumpy Jaw Disease/ Macropod Progressive Periodontal Disease (MPPD) in Macropods (kangaroos)
- Clostridial vaccines in different species of herbivores
- *Shigella* vaccines in apes
- Vaccines against chlamydial and viral infections in psittacines birds.

Autogenous vaccines have also been used for reptiles. Reports are available for lizards, turtles and snakes. *Devriesea agamarum* is a bacterium which causes chronic proliferatice dermatitis and septicemia in desert-dwelling lizards. Hellebuyck et al. (2014) used successfully an inactivated autogenous vaccine. Other authors used vaccines against paramyxoviruses in snakes (Jacobson et al. 1991) and herpesviruses in tortoises (Marschang et al., 2001).

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