Bioveterinary Research

Top level veterinary and biomedical research
for animal and public health

WAGENINGEN
UNIVERSITY & RESEARCH

'The research we conduct in our unique laboratory facilities in Lelystad contributes to healthy animal husbandry and reduces the risks of animal and human diseases.'

Ludo Hellebrekers
Director Wageningen Bioveterinary Research

Wageningen Bioveterinary Research contributes to the prevention, eradication and control of animal infectious diseases through research, diagnostics and consultancy. By doing so, we contribute to the health and well-being of animals and people.

Wageningen Bioveterinary Research conducts research on health and infectious diseases e.g. in preclinical and clinical studies, animal models, epidemiology and risk management. The results of this research and analyses have been utilised to support dossiers submitted to regulatory authorities in Europe and the US.

Our expertise is continuously expanding through ongoing research projects for private and public stakeholders on topics such as antibiotic resistance, vaccine development, gut health and vector-borne diseases. For this, we use our unique facilities in Lelystad that house livestock individually or in groups up to human Biosafety Level 3 and veterinary Biosafety Level 4.

This booklet presents examples from our research themes such as animal and public health/animal diseases, (pre)clinical studies and vaccine development. The prevention and control of animal diseases contributes to healthy animal husbandry and reduces the risks of animal diseases for humans.

Ludo Hellebrekers
Director Wageningen Bioveterinary Research

The Netherlands

- 12 million swines
- 100 million poultry
- 1,5 million dairy cows
- 1 million veal calves
- 1,5 million sheep and goats
- 6 million pets
- 500.000 horses
- A large wildlife population

Source: Ministry of Agriculture, Nature and Food Quality, 2016: Veterinary system in the Netherlands

The strength of the Netherlands

The Netherlands is the second largest exporter of agricultural products in the world. This is where a small country shows its place in the world. In 2017 the export value of food and flowers was €85,5 billion. That's 20% of the country's total export and almost 10% of gross national product.

Wageningen University & Research is continuously pulling the agricultural sector and the food processing industry to a higher level. Research and innovation helps the sector to hold its position.

By offering high quality routine analyses and providing innovative solutions to veterinary and biomedical research questions, Wageningen Bioveterinary Research helps to guarantee international trade and to preserve the international top position of the Dutch livestock industry.

Healthy livestock farming

The prevention and control of animal diseases helps to ensure healthy livestock farming and reduces the risk of infection among humans. Effective diagnostics of animal diseases is an essential part of this.

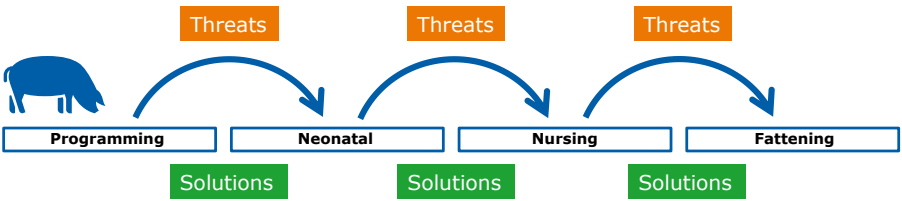
Healthy livestock farming

Wageningen Bioveterinary Research can carry out many different tests to show the presence of animal diseases. As the national reference laboratory for notifiable animal diseases in the Netherlands we perform 300,000 tests per year on horses, livestock, wild fauna, fish, crustaceans and shellfish. Of these, about 7,000 tests are used when there is a suspicion of a highly infectious disease with a disclosure requirement.

We are available 24/7 for diagnostics in the event of suspicion of important notifiable animal diseases. This enables a quick and effective response to animal diseases to ensure that the consequences for animal and public health remain as limited as possible. Thanks to effective disease control, research and diagnostics, many animal diseases are no longer present in the Netherlands.

Threats

- *Escherichia coli*
- *Streptococcus suis*
- PRRSV
- PCV2
- Mycoplasma spp.



Solutions

- Neutriceuticals/feedceuticals
- Increased vaccine efficacy
- Maternal programming
- Immunomodulation
- Management measures

Resilience – improving animal health

The prevention of diseases and the promotion of animal health play an important role in the development of sustainable animal production. Animal diseases and especially zoonoses have a tremendous impact on society. And a healthy herd is economically beneficial.

Wageningen Bioveterinary Research investigates how animal diseases can be prevented by giving young animals a good start and increasing the overall resistance of animals. Good general resistance ensures better animal welfare. In addition, robust animals are less susceptible to infectious diseases. This reduces the need for treatment and therefore the use of antibiotics.

Although attribution of the use of antibiotics in the animal domain to human anti-microbial resistance problems is relatively marginal, decreasing the use of antibiotics in animals reduces resistance in bacteria and in this way decreases the overall perseverance of resistance in our society.

Decreasing the risk of resistance

Antibiotics are a type of medicine that kill bacteria or stop them from multiplying, giving the body's own immune system the chance to fight the infection. Frequent use of antibiotics in humans and animals can involve risks. Bacteria can become resistant and pass on their resistance to future generations, making infections harder to treat. This is a problem especially for vulnerable people.

Although antibiotic use in animals has declined sharply since 2009, and the number of resistant bacteria found in animals has also decreased, research remains important. Wageningen Bioveterinary Research collects data on the effects of the use of antibiotics in animals and investigates the dynamics of resistance genes to understand how to prevent transmission within the animal domain and to humans. With this knowledge we advise policymakers and other stakeholders on how they can effectively and efficiently prevent the spread of anti-microbial resistance.

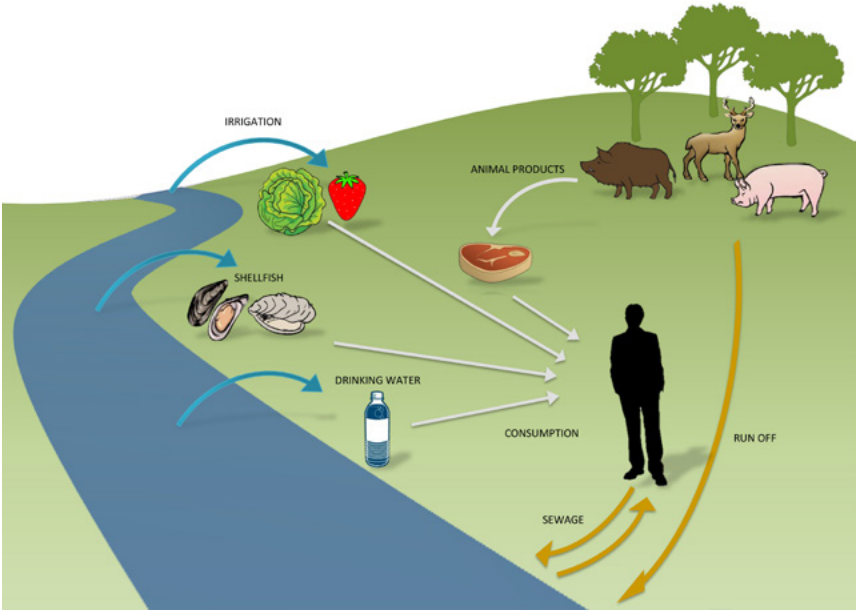
Preparing for emerging zoonoses

Pathogens in animals will continue to emerge and re-emerge throughout the world. A significant number of these pathogens may jump to humans.

Preparing for emerging zoonoses

About 70% of all known infectious diseases and ‘new’ emerging infectious diseases in humans are zoonotic. To improve preparedness for emerging and re-emerging zoonoses, Wageningen Bioveterinary Research has developed techniques for rapid detection of new and emerging pathogens in animals. We continue to work on improving these techniques with a special focus on innovative molecular methods to identify and characterise these pathogens.

In addition to optimised detection, a rapid risk assessment of potential microbiological hazards is necessary to adequately control new and emerging diseases. Therefore, Wageningen Bioveterinary Research has developed a structured approach together with partners from the animal and public health domain. In this way new and emerging infectious diseases can be combated quickly and adequately, to safeguard the health of animals and humans. The strength of our approach has been illustrated by the rapid response to the outbreak of Schmallenberg virus a few years ago.


IRRIGATION
ANIMAL PRODUCTS
SHELLFISH
DRINKING WATER
CONSUMPTION
RUN OFF
SEWAGE

Tackling transmission routes of Hepatitis E

According to the World Health Organization, 20 million people become infected with Hepatitis E (HEV) worldwide every year. There are more than three million acute cases and 57,000 deaths from HEV infections per year.

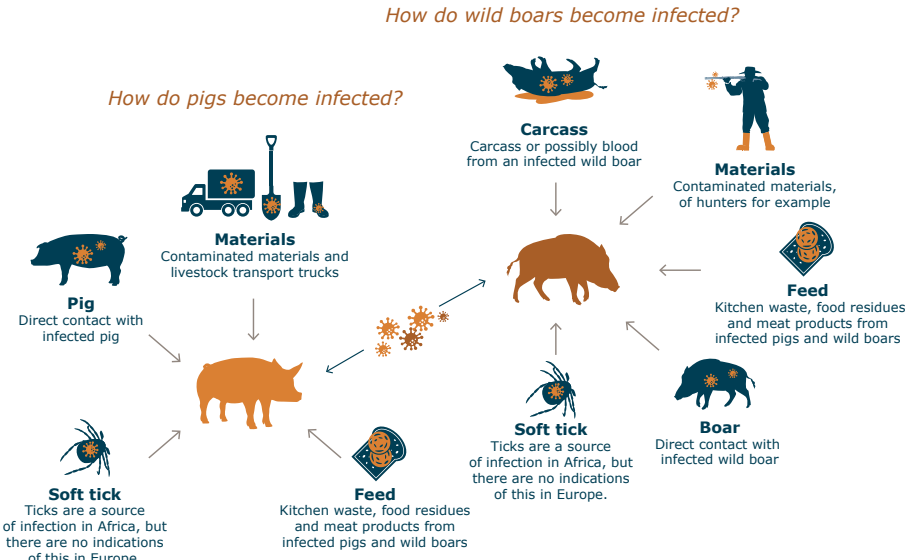
Pigs show no signs of disease when contaminated with this virus. An HEV infection in humans also usually occurs without symptoms, but for people who already have a medical condition, an infection can have serious health implications, such as liver failure and even death.

Research has shown that HEV is present in 50% of the fattening pig farms and that this contamination level remains stable. Much is still unknown about the exact route of transfer between pig farms and from pigs to humans. Wageningen Bioveterinary Research unravels these transmission routes and looks at contamination levels in surface water and meat products in which raw pork livers are processed. This knowledge is crucial to reduce the burden of disease and the risks of HEV for people.

Fighting bird flu with big data

Every year mild bird flu is detected in the Netherlands in poultry farms, especially in free-range farms. During the last outbreak of avian influenza in the Netherlands, tens of thousands of chickens were culled to prevent the virus from spreading. But there is always a risk that a virus mutates in such a way that it can be transmitted between people, leading to a global flu epidemic.

Our researchers unravelled the genetic code of the virus and combined it with big data: stacks of information about virus strains and farm data. In this way the source of the last bird flu outbreak could quickly be traced back to migrating water fowl. It became clear that there was no transmission between farms, but that the infections took place independently of each other. This is vital information that allows the authorities to take appropriate measures for an effective control of the disease.


How do wild boars become infected?
How do pigs become infected?
Carcass
Carcass or possibly blood from an infected wild boar
Materials
Contaminated materials, of hunters for example
Materials
Contaminated materials and livestock transport trucks
Pig
Direct contact with infected pig
Feed
Kitchen waste, food residues and meat products from infected pigs and wild boars
Soft tick
Ticks are a source of infection in Africa, but there are no indications of this in Europe.
Soft tick
Ticks are a source of infection in Africa, but there are no indications of this in Europe.
Boar
Direct contact with infected wild boar
Feed
Kitchen waste, food residues and meat products from infected pigs and wild boars

Combating African swine fever

African swine fever is spreading from Eastern Europe. Wild boars play an important role in this process.

Depending on the pathogenicity of the virus, 30% to 100% of the infected animals die. Pigs can survive the acute phase and appear to have recovered, only to become long-term carriers of the virus.

Dutch authorities are taking measures to prevent an outbreak. Wageningen Bioveterinary Research coordinates the national monitoring program for wild boar and all laboratory tests are done in our High Containment facilities. Yearly about 2000 samples are collected for analysis of antibodies to swine fever and Aujeszky's Disease. In the event of suspected cases of African swine fever, Wageningen Bioveterinary Research will test samples immediately by order of the Netherlands Food and Consumer Product Safety Authority (NVWA).

Psittacosis, improving disease control

It looks like flu, affects pigeons and chickens in addition to parrots and is quite unknown: parrot fever or psittacosis. People too can get infected sometimes resulting in severe pneumonia if they inhale dust particles infected with the bacterium *Chlamydia psittaci* that causes psittacosis, for example when cleaning a cage.

Wageningen Bioveterinary Research is working with national partners from the public and animal health domain on research to improve disease control via an online *One Health* platform that incorporates information about human and animal cases. This improves connecting human cases to their animal source. This way the animal source can be controlled more effectively.

Healthy aquaculture

Fish production via aquaculture is increasing strongly worldwide. In 2015, this was approximately 70 million tons, comparable to the annual yield from the fishery, but already higher than beef production. The expectation is that fish farming production will come close to that of chicken (90 million tons) and pig (100 million tons) within the foreseeable future.

Healthy aquaculture

One of the threats to intensive aquaculture is the occurrence of contagious fish, crustacean and shellfish diseases, which can cause serious illness and death and thereby economic losses.

Wageningen Bioveterinary Research has a specialised fish and shellfish disease laboratory where accredited and rapid diagnostics are performed to identify new outbreaks at an early stage.

This is the one complete disease laboratory in the Netherlands for fish cultured for human consumption, ornamental and wild fish and shellfish. Wageningen Bioveterinary Research thus makes an important contribution to healthy fish in healthy aquaculture and thus to safe and healthy fish products for human consumption.

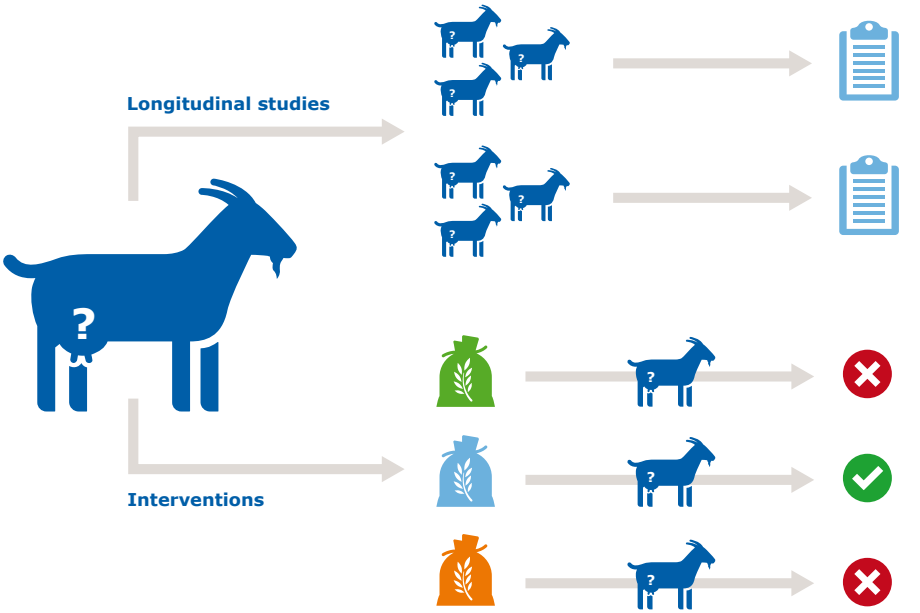

JOHN DEERE
9600

Disinfectant testing

According to European law and regulations (NEN 14675), disinfectants are generally tested for their ability to inactivate a bovine enterovirus. However, it does not identify the effects on specific viruses. An important field of application of disinfectants on farms is to prevent spread of infections of notifiable diseases, such as the current urgent threat for African swine fever (ASF), foot-and-mouth disease (FMD), and avian influenza (AI).

Throughout such outbreaks, the cleaning and disinfection of all materials, equipment and housings play an essential part in the containment of the disease. In addition, transport vehicles visiting contaminated farms or areas need to be cleaned and disinfected systematically to prevent the spread of infectious diseases.

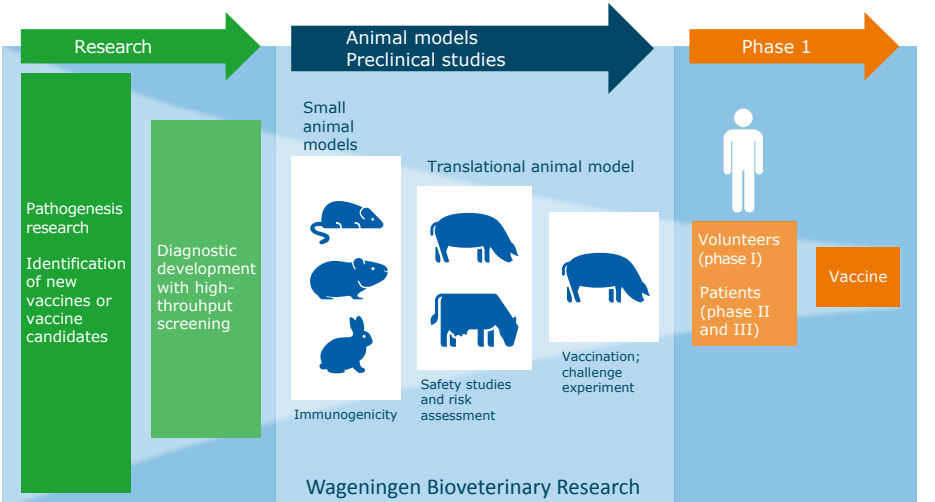
Wageningen Bioveterinary Research (WBVR) is able to test disinfectants according to the NEN 14675 norm, using our unique veterinary BSL4 facilities and the specific viruses. Product positioning will strongly gain power by proving its efficacy to kill specific viruses.


Longitudinal studies
Interventions

Optimising udder health

Dairy cattle farmers want healthy animals and good milk production. Udder health is an important part of this. Bacteria that penetrate udders can cause infection. Udder infections are easy to treat, but they account for the majority of antibiotic use. There's also a negative impact on milk quality. Fending off bacteria is therefore very important both for the cattle and the dairy farmers.

Wageningen Bioveterinary Research is carrying out research into the various ways in which bacteria enter the udder. In cows, bacteria usually enter the udder through the teat orifice. It's not clear whether the same is true for goats. We're currently working with various partners in the dairy goat farming sector to better understand the possible causes of high levels of bacteria in udders. This understanding will then guide research into other areas such as the use of nutritional interventions as a way of improving udder health and possibly minimising the use of antibiotics.


Research
Pathogenesis research
Identification of new vaccines or vaccine candidates
Diagnostic development with high-throuhput screening
Animal models
Preclinical studies
Small animal models
Immunogenicity
Translational animal model
Safety studies and risk assessment
Vaccination; challenge experiment
Wageningen Bioveterinary Research
Phase 1
Volunteers (phase I)
Patients (phase II and III)
Vaccine

Animal models

Before medicines become available to people, they must be extensively and thoroughly tested. The law prescribes research to ensure the safety of new drugs. For this reason, it is mandatory to test new medicines on animals in laboratories before they can be placed on the market.

Many animals are genetically surprisingly similar to humans. They have the same organs performing the same functions in the same way. Nearly 90% of the medicines used in animals for treatment can be used in the same or a similar way for humans. Animal studies make a vital contribution to the understanding, treatment and prevention of diseases in both animals and humans.

Wageningen Bioveterinary Research develops animal models to address these societal needs and tests new vaccines in animal models. We carry out these tests in accordance with legal requirements and the highest possible standards for animal welfare. We are guided by the principle of the 3 r's: replacement, reduction and refinement.

Alternative tests

Wageningen Bioveterinary Research does research aimed at finding alternatives for research with laboratory animals.

Botulism is caused by a toxin produced by the bacterium *Clostridium botulinum*. Botulism is a rapid onset, usually fatal disease that can cause paralytic symptoms in livestock, waterfowl and birds, which may lead to death.

Traditionally, mice are used to test for botulism. Research by Wageningen Bioveterinary Research, together with European partners in this area, has led to the development of an alternative test for diagnosing botulism. The number of mice used in tests for botulism has thus decreased by as much as 90%.

Respiratory infections (RSV) in children and calves

Although a Respiratory Syncytial Virus (RSV) infection usually manifests itself as a common cold, it can lead to serious bronchitis or pneumonia in young children.

Intensive medical care can help children to survive serious infections, but about 200,000 children throughout the world die annually from this infection. Unfortunately, there is no vaccine or precise treatment yet available to prevent or combat an RSV infection.

Related to the disease in calves
The human RSV is closely related genetically to a variant of the virus that occurs in calves with respiratory problems. Because the progress of the infection is similar, calves are being studied to better understand the infection process and develop effective and safe intervention strategies.

Developing safe intervention strategies
The research on calves by Wageningen Bioveterinary Research (WBVR) contributes to the development and evaluation of vaccines and therapies for both children and calves. The resulting intervention strategies can help to reduce deaths and serious respiratory problems in people and animals worldwide.

Safety of animal products

TProcessed animal intestines are used to make edible sausage casings. "Natural casings" are traded worldwide and may come from areas where notifiable infectious animal diseases are prevalent, such as foot and mouth disease, classical swine fever or African swine fever.
Natural casings generally consist of a thin collagen-rich layer which is part of the intestines from pigs, cattle, sheep or goats. Before use, the casings are preserved by salt treatment in accordance with European guidelines.

Outbreaks of animal diseases can occur when contaminated products unintendedly enter the food chain. That is why the salt treatment must be shown to be undeniably effective in inactivating these various viruses.

Researchers at Wageningen Bioveterinary Research, have developed an in-vitro 3D model that simulates a natural casing. This model can be used to predict and validate the outcome of decontamination procedures without requiring animal testing, available for industrial application. This innovative approach reduces the experimental animal use, contributes to the safety of these animal products and helps to prevent outbreaks of notifiable animal diseases.

Photo: Anais Callens

Vaccine development

The use of vaccines is one of the most powerful options in the prevention of animal diseases. Wageningen Bioveterinary Research has extensive experience in the field of vaccine development. In the past we have developed a number of very successful vaccines against, for example, Aujeszky and Infectious Bovine Rhinotracheitis. As a contract research organisation, we develop vaccines against viral and bacterial diseases together with external parties.

The biggest drawback of vaccination is that vaccinated animals and products can normally not be distinguished from natural infected ones, which hampers the actual control of the disease and the trade in animal products. Our institute is leading in developing so-called DIVA vaccines. DIVA vaccines do not have this disadvantage because for these vaccines diagnostics are developed that can distinguish between vaccinated and naturally infected animals.

Vaccine against Bluetongue virus

Several years ago, an outbreak of the Bluetongue virus (BTV) in The Netherlands caused disease, paralysis, deformed offspring and death of sheep and cattle. The economic damage amounted to tens of millions of euros. It is only a matter of time before the next outbreak must be faced.

Wageningen Bioveterinary Research developed an innovative prototype vaccine which is expected to be more effective than vaccines that are currently available. Furthermore, the new vaccine can be easily adapted to new virus strains. This would mean this disease can be controlled more rapidly.

Vaccine against Rift Valley fever

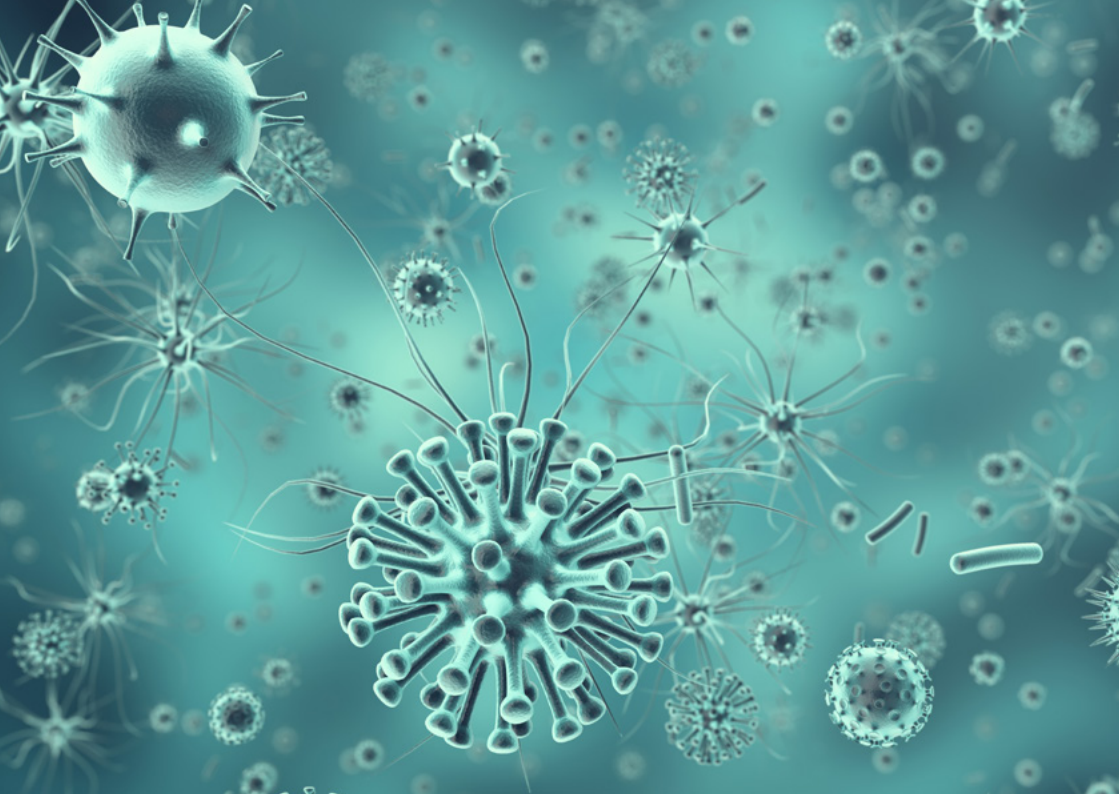
Rift Valley fever virus is a mosquito-transmitted virus causing mortality among farm animals. It is one of the 8 pathogens on the World Health Organisation's list of 'top-emerging diseases that are likely to cause major epidemics'. The virus is currently circulating on the continent of Africa but also presents a risk to other continents, including Europe.

Wageningen Bioveterinary Research developed a live-weakened vaccine that is optimally designed for safety and effectiveness. The vaccine will be further developed together with the industry to achieve effective control of Rift Valley fever.

Vaccine against *Streptococcus suis*

Streptococcus suis is a bacterium that threatens the health and well-being of pigs. *S. suis* infections are one of the most common reasons for the use of antibiotics in pig farming, particularly around weaning age. *S. suis* can cause serious symptoms and lead to meningitis, joint inflammation, blood poisoning and even death.

Currently there is no vaccine available that effectively protects against all *S. suis* infections. Vaccines based on killed *S. suis* bacteria only protect against the same serotype. Because there is a great need for a vaccine that protects against the most important serotypes, Wageningen Bioveterinary Research is collaborating closely with industry to develop such a vaccine.



New Vaccine technology

Biotech company BunyaVax focuses on the rapid development of vaccines based on a promising new vaccine technology developed and patented by Wageningen Bioveterinary Research. This technology is based on virus particles that are capable of infecting cells only once, so called replicon particles.

The vaccine platforms are now used to generate vaccine candidates against several infectious diseases. BunyaVax is also exploring the application of these platforms for developing cancer immunotherapies. Proof of concept was already demonstrated for Rift Valley Fever, influenza and lymphoma.

The platform can be used to develop vaccines within weeks after the emergence of a new pathogen – which is highly valuable in case of an impending epidemic.

More information: www.bunyavax.com

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Wageningen Bioveterinary Research collaborates with public and private partners to safeguard animal and public health through prevention, eradication and control of animal diseases. Wageningen Bioveterinary Research is part of Wageningen University & Research.

The mission of Wageningen University & Research is to explore the potential of nature to improve the quality of life. Our strength lies in our ability to join the forces of specialised research institutes and the university in the fields of natural and social sciences.
This collaboration leads to scientific breakthroughs that can be put into practice and be incorporated into education. This is the Wageningen Approach.

For more information:
www.wur.eu/bioveterinary-research