# Disease control tools to secure animal and public health in a densely populated world

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**Animal health is a prerequisite for global health, economic development, food security, food quality, and poverty reduction, while mitigating against climate change and biodiversity loss. We did a qualitative review of 53 infectious diseases in terrestrial animals with data from DISCONTOOLS, a specialist database and prioritisation model focusing on research gaps for improving infectious disease control in animals. Many diseases do not have any appropriate control tools, but the prioritisation model suggests that we should focus international efforts on Nipah virus infection, African swine fever, contagious bovine pleuropneumonia, peste des petits ruminants, sheeppox and goatpox, avian influenza, Rift Valley fever, foot and mouth disease, and bovine tuberculosis, for the greatest impact on the UN's Sustainable Development Goals. Easy to use and accurate diagnostics are available for many animal diseases. However, there is an urgent need for the development of stable and durable diagnostics that can differentiate infected animals from vaccinated animals, to exploit rapid technological advances, and to make diagnostics widely available and affordable. Veterinary vaccines are important for dealing with endemic, new, and emerging diseases. However, fundamental research is needed to improve the convenience of use and duration of immunity, and to establish performant marker vaccines. The largest gap in animal pharmaceuticals is the threat of pathogens developing resistance to available drugs, in particular for bacterial and parasitic (protozoal, helminth, and arthropod) pathogens. We propose and discuss five research priorities for animal health that will help to deliver a sustainable and healthy planet: vaccinology, antimicrobial resistance, climate mitigation and adaptation, digital health, and epidemic preparedness.**

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## Introduction

Our world is transforming at an unprecedented rate, with climate change, increasing demand for resources, and biodiversity loss arguably being the most prominent challenges for human societies in future decades.[1,2] Population growth and escalating human activity have become the main drivers of these global challenges, upholding society under permanent change itself. Megatrends of urbanisation, changes in land use, globalisation of trade and movements, and evolving consumer behaviour with a globally increased demand for animal-based proteins are inducing profound changes to the global food system, not least in livestock systems.[3] Existing food systems are highly divergent between countries, either not producing foods essential for healthy diets in sufficient quantity and quality at an affordable price, or producing large quantities of food at the expense of driving degradation of the natural environment, biodiversity loss, and climate change.[4–6] Actual and perceived links between livestock and land use, climate change and biodiversity, and food security and human health are shaping global policies and research agendas, such as the European Green Deal.[7] Animal health will be key to support a transition towards resource-efficient, healthy, and environmentally sustainable food systems with high animal welfare standards. Livestock health is a prerequisite for global health, economic development, food security, food quality, and poverty reduction,[8] while mitigating against climate change[9] and biodiversity loss.[10] Reducing the burden of animal diseases, including zoonoses, and appropriately managing emerging diseases, pandemic threats, and antimicrobial and antiparasitic resistance, are considered priorities to achieve sustainable livestock systems.[11,12] Many animal diseases lack do not have any specific control tools, and the animal health solutions that are available require continuous innovation to address issues like changing animal husbandry practices, consumer expectations, residues in food or the environment, drug resistant pathogens, and correct implementation by the end user.[13]

DISCONTOOLS (Disease Control Tools)[14] is an open access database created to support funders of animal health research in identifying important gaps and challenges in infectious disease control in animals, and to speed up the delivery of new diagnostics, pharmaceuticals, vaccines, and control strategies, with the overall goal of reducing the global burden of animal diseases. Created in 2008, with funding from the Seventh Framework

### Key messages

- We did a qualitative review on the research gaps around 53 infectious diseases in animals
- We identified animal diseases with greatest potential for impact on UN Sustainable Development Goals
- There is a pressing need to increase and sustain fundamental and applied research into diagnostic development, vaccinology, digital health, therapeutics, and control strategies
- Increased research on animal health is a prerequisite to address global issues, such as food security, climate change, antimicrobial and antiparasitic resistance, and epidemic preparedness

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Programme of the European Union, it contains information for more than 50 infectious animal diseases or pathogens and receives support from individual countries and the animal medicines industry. With the support of the STAR-IDAZ International Research Consortium on Animal Health, DISCONTOOLS has evolved to a database for global use, in which more than 400 experts from academia, government, and industry have contributed to research gap analyses for specific diseases. However, to support global research policies, research coordination, and highly ambitious research and innovation programmes, an overarching analysis is needed to identify the areas in which the largest impact for a healthy and sustainable planet might be achieved. We did a qualitative analysis of 53 DISCONTOOLS disease chapters to identify the major research needs. Within each disease category, we first evaluated whether particular disease complexes should be prioritised. Then we scrutinised the existing state of knowledge and available control tools to identify the diagnostic, vaccine, and pharmaceuticals gaps, in which research and innovation could mean a big advance in animal disease control. We conclude by proposing five priority research themes that would help to achieve a healthy planet via animal health solutions.

## Priority diseases

Infectious animal diseases can broadly be divided into three disease categories: epizootic, zoonotic, and enzootic, with each category leading to different decision routes and control measures. Epizootic (corresponding to epidemic in human medicine) diseases are sometimes referred to as transboundary diseases; they include panzootic and some zoonotic diseases, typically have sudden, often fatal effects, and affect trade. The control of epizootic diseases is mostly subjected to national and international control measures (eg, obligatory surveillance systems, test procedures, and culling policies for Rift Valley fever and African swine fever). Zoonotic diseases (eg, brucellosis or tuberculosis) can be transmitted between animals and humans via food or direct or indirect contact with infectious individuals, with their control mostly regulated by public health authorities. Enzootic diseases, always present in animal populations and often caused or exacerbated by management, housing, or nutritional factors, can seriously affect efficient livestock production. Compared with epizootic diseases and many zoonotic diseases, enzootic diseases are subject to less stringent regulations and their control remains largely under the responsibility of the individual farmer.[15] They are also referred to as production diseases or food-producing animal complexes.

See **Online** for appendix

Although some diseases can fit into more than one category, and classification is heavily influenced by the animal health status of a region or country, each of the 53 diseases was assigned a category and ranked by total score, attributed by a prioritisation model (appendix p 1). Prioritisation models of human or animal diseases have existed for more than two decades. In animal diseases, most prioritisation exercises have been done to evaluate the risk related to zoonotic pathogens, although separate exercises are available for prioritisation of exotic threats, non-regulated animal infectious diseases, and wildlife pathogens.[14] The approach applied here allows for the evaluation and comparison of diseases within particular categories, taking into account their specific impact on stakeholders and the different decision-making processes involved.

We ranked DISCONTOOLS diseases by total prioritisation score (figure 1). The order of some diseases has changed since the original launch of the database in 2012.[14] However, the diseases listed in the top five have remained the same. The high ranking of African swine fever was considered surprising at the time, but its importance has been supported by outbreaks in Europe (since January 2014) and China (since August 2018). The DISCONTOOLS prioritisation model supports research for increased preparedness and collaboration between countries for diseases such as Nipah virus infection, Rift Valley fever, and peste des petits ruminants (also known as ovine rinderpest). All these diseases have rarely or never been detected in Europe, but there is a constant threat of pathogen introduction from endemic regions.

We applied the prioritisation model using only the scoring criteria with direct relevance to the Sustainable Development Goals[16] and the EU's Green Deal Agenda:[17] impact on animal health and welfare, human health, security of the food supply, and the ability to spread in humans and economic impact. The use of these scoring criteria resulted in a different disease ranking, with a top-five listing of contagious bovine pleuropneumonia and classical swine fever and a top-ten listing of avian influenza, and sheeppox and goatpox, with orthopox and parapox, bovine spongiform encephalopathy, and trypanosomiasis decreasing in rank.

Several diseases have appropriate control tools available (figure 1). Marker vaccines and associated diagnostics have facilitated successful control programmes for infectious bovine rhinotracheitis in many countries,[18] and the global eradication of sheeppox and goatpox is considered achievable with the existing vaccines.[19] The need for improved tools is highest for zoonotic diseases (appendix p 4). There is also a gap in vaccines for production diseases and fit-for-purpose pharmaceuticals for epizootic diseases (appendix p 4).

## Diagnostic gaps

Fast, easy-to-use, and accurate diagnostic methods are available for many animal diseases. However, there is an urgent need, shared across diseases, for the development of stable and durable diagnostics that can differentiate infected from vaccinated animals (DIVA; figure 2; panel). There are important challenges around exploiting rapid technological advances in a timely manner and making diagnostics available and affordable to all, similar with

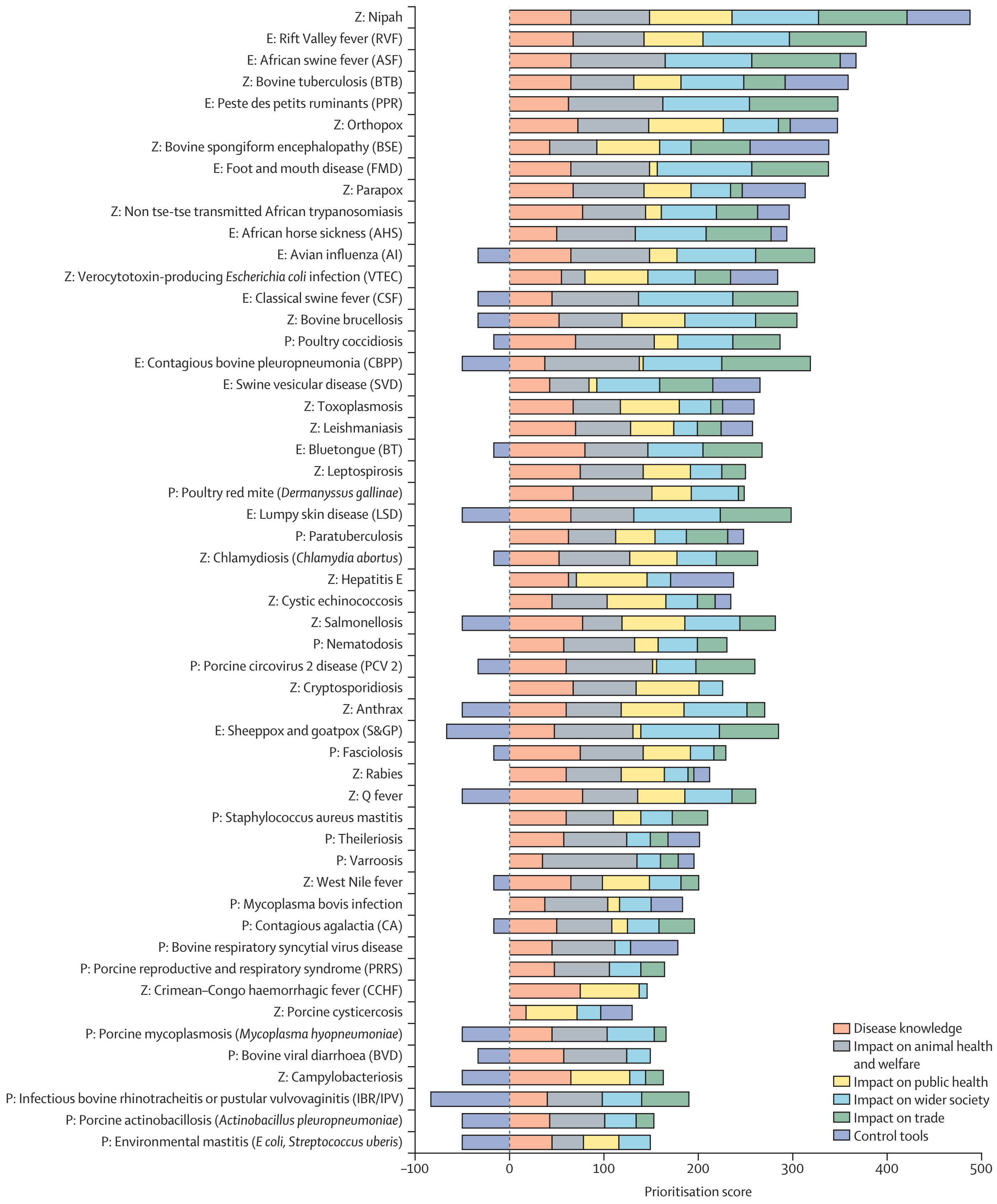

*Figure 1:* **DISCONTOOLS diseases ranked by total score**

Colours indicate relative impacts on the total disease score of the different scoring criteria in the prioritisation model. A negative score for control tools means relatively low need for improved control tools. Some categories overlap. E=epizootic disease. P=enzootic or production disease. Z=zoonotic disease.

the challenges associated with the use of diagnostics for humans in resource-constrained settings.[24]

In epizootic diseases, late detection and undetected infections are key obstacles to containment. Control would benefit from more affordable diagnostics and increased attention to production capacity and strategic reserve. Other common needs across epizootic diseases include the demand for more molecular diagnostics (ie, differentiating strains and detecting new variants), harmonisation, and validation with the availability of

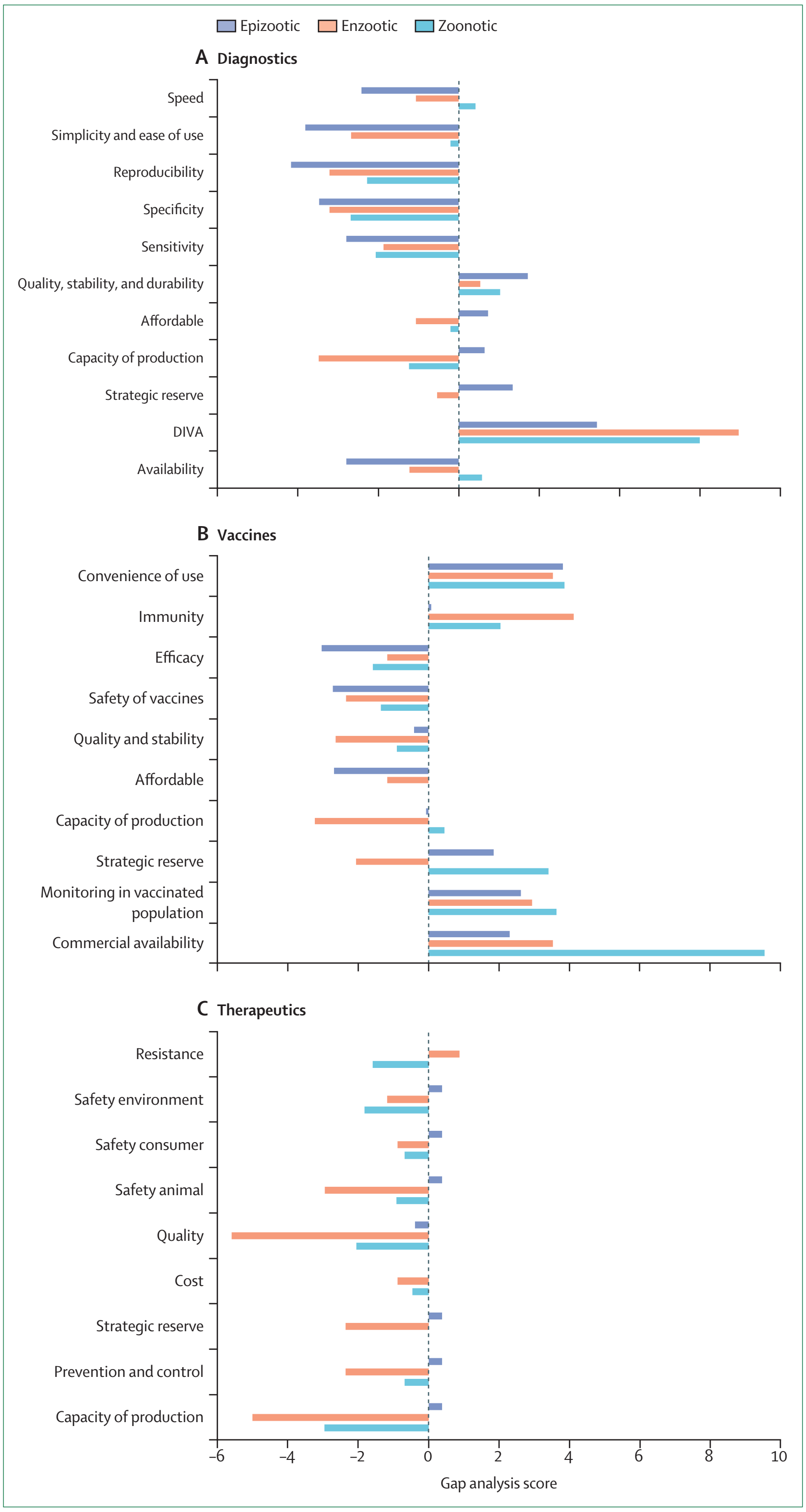

***Figure 2:* Gap analysis scores for diagnostics, vaccines, and therapeutics**
Negative *vs* positive scores indicate no or a relatively low *vs* a high need to improve or develop the listed control tool characteristic. DIVA=differentiate infected from vaccinated animals.

high-quality reference panels and interlaboratory proficiency schemes. Active surveillance to detect silent circulation and adaptive diagnostic capacity for finding new viral recombinants are essential for accurate diagnosis and a quick response against new disease threats and pathogens of high evolution rate and genetic variability. The benefits of surveillance have been testified by the retrospective detection of swine enteric coronaviruses in Europe,[25] the emergence of porcine deltacoronavirus in the USA[26] and China,[27] and the rapid spread of the highly pathogenic strain of the porcine reproductive and respiratory syndrome virus throughout southeast Asia.[28] Further development of laboratory-based or institutional-based diagnostics into validated commercial kits would enhance availability and wider use of diagnosis. DIVA tests are required for many vaccine-preventable diseases, including African horse sickness, avian influenza, classical swine fever, contagious bovine pleuropneumonia, and peste des petits ruminants. Point-of-care diagnostics can make an important contribution to affordability and upscaling diagnostic capability.[29] However, concerns about integration of these diagnostics into diagnostic workflows of official surveillance and control programmes need to be addressed through digitalisation and sociological and managerial innovations to improve user training, test distribution, and data control from point-of-care to risk manager.

For enzootic diseases, various diagnostic tools are commonly available. However, because causative pathogens are often commensal organisms and widely prevalent, the diagnostic value of tests that solely show the organism's presence or absence is low. In some parts of the world, including Asia and Africa, access to standardised validated tests can be poor, mostly because of costs and the absence of surveillance systems in which diagnostics can be applied. Therefore, there is a need for diagnostics that go further and can differentiate between prevailing species, genotypes, or serotypes distinguish infective versus non-infective stages; inform disease impact assessments on animal production and welfare; and be used outside of traditional surveillance systems. For example, gastrointestinal nematode infections in cattle can be caused by a mixture of up to 20 different nematode species. New diagnostics that assess whole species composition or have thresholds defining the impact of infection on productivity are shaping new control approaches.[30,31] DIVA tests are required for diseases or infections, such as poultry coccidiosis, salmonella infections in swine, and infections with bovine respiratory syncytial virus and bovine viral diarrhoea virus. We need a better understanding of the factors that drive users to adopt diagnostic approaches in disease prevention, with full exploitation of social science theories.[32,33] (appendix p 2).

In zoonotic diseases, a common obstacle to the development of diagnostic tools is the absence of a diagnostic market. In many cases, diagnostics are available or could be developed but the incentives for market development have not yet been created through awareness and demonstration projects, economic viability studies, and policy interventions. For example, diagnostics (and vaccines) for enterohaemorrhagic *Escherichia coli* infections are increasingly available. However, they are only useful if they can contribute to early food chain interventions to prevent transmission to humans, whereas there are no direct animal health benefits.[34] The implementation of these tools is delayed by conflicting responsibilities of veterinary and public health agencies, economic drivers, and because clinical trials testing interventions across species boundaries are highly challenging to achieve.[35] Several zoonotic diseases do have a substantial economic impact at the farm level, but these costs are mostly related to imposed control measures.[36,37] In some cases, detailed field studies to quantify deleterious effects on animal health and performance in addition to the public health burden (eg, salmonellosis in pigs) could probably support development of diagnostics and control measures at farm level.[38] Diagnostic tools are needed not only to detect zoonotic pathogens in animals, but also to establish pathogen viability, infectiousness to humans, and to detect environmental contamination in cases such as Q fever.

Diagnostic research is a rapidly changing field. Technological advances in the form of miniaturised platforms for whole genome and proteomic analysis, artificial intelligence, biomarkers for health, sensors, and big data approaches are reshaping the way diseases are detected and controlled.

Next-generation sequencing technology, or high-throughput sequencing, has become a powerful tool to integrate several applications into the routine of veterinary laboratories: from accurate detection and characterisation of pathogens to screening for presence of antimicrobial resistance mutations or genes, vaccine escape variants, recombination or reassortment, and virulence and pathogenicity factors. Whole-genome sequencing can have a very high discriminatory power and can be used in the routine workflow for typing of pathogens in outbreak investigation, surveillance, transmission, and diagnosis. The analysis of pathogen genomes can shed light on pathogen spread, contact tracing, dynamics of epidemics, times of infection, and geographical origins of pathogen emergence. Once suitable molecular markers are identified with sequencing, they can rapidly be used in a targeted, multi-locus, deep amplicon sequencing approach for routine molecular surveillance. These markers are already used to track viral and bacterial infectious outbreaks, but the use of genome sequencing in parasites is still in its early development, because their genomes are larger and more complex.

The digital revolution not only drives simultaneous detection of multiple causative pathogens of a disease syndrome, but also enables faster point-of-care diagnosis and helps to encompass broader disease determinants in diagnosis and monitoring.[40] Systems for (permanent) monitoring of animal behaviour (eg, activity level, daily feed, and water intake), clinical signs (eg, automated cough monitoring in pigs) and environmental parameters (eg, temperature, relative humidity, air velocity, concentration of stable gases) will support the development of dynamic, integrative, and holistic approaches for animal disease prevention. Digital technologies could be divided into (1) wireless and mobile applications for animal health monitoring, disease surveillance, reporting, and information sharing; (2) big data and analytics approaches to detect patterns and make predictions; and (3) technologies such as blockchain applications for efficient management of supply chains, including therapeutics and vaccines.[41] Converting the large amounts of generated data into knowledge and improved decision-making support, while keeping animal disease diagnosis affordable and available for all, will be a challenge. It will be crucial for veterinary services to invest in new technologies and equip the veterinary workforce with the necessary digital skills through education.[41]

**Panel: Common diagnostic gaps for each disease category in the DISCONTOOLS database**

- Harmonisation and validation: epizootic (including panzootic) and enzootic
- Reference panels: epizootic (including panzootic) and enzootic
- Integration of pen-side tests in diagnostic workflows: epizootic (including panzootic)
- Structured monitoring schemes: enzootic
- Differentiate infected from vaccinated animals tests: epizootic (including panzootic), zoonotic, and enzootic
- Molecular diagnostics: epizootic (including panzootic)
- Diagnostics for transmission potential and environmental contamination: zoonotic
- Diagnostics that differentiate between species genotypes and stages of disease: enzootic
- Commercial kits: epizootic (including panzootic)
- Diagnostics that support intervention strategies in animal reservoir: zoonotic
- Diagnostics that assess the impact of disease on animal productivity: enzootic

## Vaccine gaps

Veterinary vaccines are a vital component in protecting animal and human health and are essential for dealing with new and emerging diseases.[42] They are often considered a sustainable control method because they can provide durable protection, leave no traces of pharmaceuticals in the environment, and can alleviate the need to use antimicrobials.[43] However, animal vaccine development gaps are a concern with regard to the convenience of use, duration of the induced immunity,

| | Epizootic (including panzootic) | Zoonotic | Enzootic |
|---|---|---|---|
| Target product profile | Single-shot, safe; lifelong and broad protection, multivalent vaccines; DIVA vaccines | Long lasting immunity; show relevance for animal health to stimulate farmer uptake; and DIVA vaccines | Single-shot, safe, lifelong and broad protection; multivalent vaccines; and DIVA vaccines |
| Discovery and understanding | Host immune mechanisms; identification of genes and proteins affecting virulence and immune response; and inhibitory effects of maternal antibodies | Host immune mechanisms; identification of protective antigens and virulence factors; and translate findings from mouse models into target species | Host immune mechanisms; different approaches to identification of antigens; inhibitory effects of maternal antibodies; understand effects of pathogen induced immunomodulation on vaccines; and new delivery and adjuvant systems |
| Manufacture | Incentives to produce ahead of crisis; vaccine banks for international use; coverage of new virus variants in vaccines; and alternative routes of administration for mass treatment | Cost-effective vaccines and alternative routes of administration for mass treatment | Alternative routes of administration for mass treatment and autogenous vaccines |
| Regulation | Alternatives to animal models and adaptive regulatory systems considering strain variability and emergency character | Alternatives to animal models | Alternatives to animal models |

DIVA=differentiate infected from vaccinated animal.

***Table 1:*** **Common vaccine gaps in DISCONTOOLS database along the innovation pipeline by disease category**

strategic reserve to deal with outbreaks, DIVA performance, and commercial availability. Most vaccine development gaps are shared across disease categories (table 1). Overall, there is an immediate need for continued research to identify the relevant protective antigens and virulence mechanisms with genomic, bioinformatic, proteomic, immunological, and biological approaches, and on delivery systems.

New vaccines are needed, with longer lasting immunity, ideally requiring only a single shot. Because of the short lifespan of a production animal (especially pigs and poultry), many vaccines would need to be administered in the first weeks of life, but inhibition with the presence of maternal antibodies is an obstacle to successful vaccination for many diseases.[44] Oral, intranasal or in-ovo vaccination can partly overcome this obstacle.[45] In particular, in-ovo vaccination offers the advantages of large scale, standardised immunisation, with no associated stress to the vaccinated animal and the potential to bypass maternal immunity. For example, in-ovo vaccination of hen eggs with Newcastle disease virus (NDV) antigens delivered in either a herpesvirus of turkeys viral vector or as a recombinant NDV vector containing sequence encoding avian interleukin-4, stimulates protective immunity in chicks, while being either only transiently affected by anti-NDV maternally derived antibodies or bypassing them entirely.[46,47]

Fundamental research into host immune mechanisms and immune evasion by pathogens is a requirement for the provision of new generation vaccines. However, most existing immunological knowledge stems from mouse models. Additional reagents, cell lines, and models to study immunology in relevant animal species are required.[48,49] Animal-free models (eg, organoids, organ-on-chip,[50] and in-silico approaches) for research and to test vaccine quality and safety before release of vaccine lots are also needed. The in-vivo assay for rabies vaccine potency testing requires the annual use of more than 70 000 mice;[51] the test is highly variable and needs to be replaced by a combination of in vitro testing and consistency monitoring. Identification of immune correlates of protection would allow efficacy monitoring in vaccinated populations and reduce the need for experimental animals. For diseases colonising mucosal surfaces (eg, *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae,* or *Campylobacter* spp.), a crucial problem is that colonisation cannot be prevented, and how to elicit an effective mucosal immunity remains unanswered. The use of edible vaccines as a method for stimulating protective mucosal immunity in the gastrointestinal tract is of interest, and such vaccines can be produced and delivered through the edible parts of plants, fruits, and vegetables; in bacteria as probiotics, in whole yeast; or within (or decorated on) liposomes, virus-like particles, nanoparticles, and immunostimulatory complexes. The aim of these methods is to survive digestion and deliver the appropriate antigens to antigen-presenting cells at the appropriate site, and to induce immunity while preventing tolerisation. The task of avoiding antigen degradation in edible vaccines is arguably easier to achieve in monogastric animals than in ruminant animals. However, a range of prototype edible vaccines has been developed for viral, bacterial, and even metazoan parasites since 1998.[52] For infections that have an effective vaccine (eg, bovine respiratory syncytial virus, West Nile virus, or *Mycoplasma hyopneumoniae*) improvements can be made by (1) developing multivalent vaccines that cover multiple or all strains of the same pathogen or even different pathogens (eg, syndromic vaccines against different pathogens involved in a similar clinical profile like neonatal diarrhoea); (2) innovating delivery methods (eg, oral, needle-free or suitable for a single mass-treatment delivery for life-long protection); (3) improving DIVA performance; and (4) developing new vaccination schedules. For vaccines that have been trialled with low success so far, such as for nematode infections, more fundamental knowledge on immune responses and immune evasion is required, and multiple and innovative approaches to engineer protective antigens.[53]

Specific needs for epizootic diseases include incentives for the medicines industry to develop, test and produce vaccines ahead of a crisis and a flexible regulatory environment that considers strain variability and the urgency for rapid market authorisation early in the outbreak of a disease. Vaccine platforms with capacity for rapid development and potential for low-cost manufacture, such as mRNA vaccines or vectored vaccines, offer new, exciting frameworks in this field.[54,55] In case of emergency, regulatory approval could be shortened with reciprocal approval or accelerated procedures for vaccines produced via platforms in which only a small component in a previously approved vaccine is changed.

Furthermore, strategic, well characterised, and widely available vaccine banks need further development and support, such as the work done by the African Union Pan African Veterinary Centre. Vaccine banks can only fulfil their role when the infrastructures for stockpiling and distribution are adequately complemented by vaccine availability (ie, with local or regional production of high-quality vaccines).[56] In enzootic diseases caused by ubiquitous pathogens, such as porcine reproductive and respiratory syndrome virus in pigs or coccidiosis in poultry, the use of vaccines is proposed to reduce the effect of the pathogen and the need for antibiotics to treat secondary infections.[43] However, further research is required to define the minimum required efficacy, long term benefits for animal health and productivity, and effectiveness in reducing antibiotic use. In zoonotic diseases, as for diagnostics, initiatives are needed for economic viability and market development to address issues of a non-existent animal health market.

Autogenous vaccines are increasingly used by many countries when other vaccines are not available,[57] but there are still no harmonised requirements for their manufacture and use.[58] The development of successful vaccines has been mostly based on empirical research with live, attenuated, or killed microorganisms, or detoxified versions of their toxins.[59] New technologies promise a change in animal vaccine development with the development of nucleic acid, subunit, peptide, or vectored vaccines, and new genome editing techniques.[60] Ebola virus and SARS-CoV-2 have shown how quickly progress can be made in emergency situations through collaboration between industry, international organisations, and governments. Closer cooperation at the global level, supported by research teams with complementary skills and public–private sector partnerships are required to bring these technologies to successful applications in animal health.[61]

## Therapeutic gaps

The animal health pharmaceutical industry has been a pioneer in the application of drug delivery technology, engineering, and biotechnology to product development.[62,63] In specific cases, veterinary drugs have also found applications in human medicine, such as the Nobel prize winning avermectins.[64] Veterinary drug development is made difficult by the diversity of species and breeds, differences in metabolism, biology and disease course, animal and user safety needs, and cost sensitivity.[62] However, from our overarching gap analysis (figure 2), there appear to be no major gaps for the development of pharmaceuticals, which could be explained by two reasons. Firstly, the absence of antivirals in animal medicine is not considered in our graph. In the EU, the use of antivirals is prohibited because of the risk of resistance development in human viruses and because they could mask virus circulation, making clinical signs less or not recognisable. These effects would complicate early disease detection and management, considering that many viral diseases are notifiable at EU and international level. Effective control of epizootic viral diseases is expected to come from vaccines, whereas anti-inflammatory drugs and antibiotics are available for supportive care and to treat secondary infections. Secondly, pharmaceuticals need to adhere to strict regulations to guarantee their efficacy, quality, and safety to the animal, environment, person who administers the drug, and consumer. Quality and safety gaps are thus already largely addressed before pharmaceuticals become available on the market. Of note is the renewed attention for ethnoveterinary preparations, particularly (but not only) in Asia and Africa, to address gaps when allopathic medicinal products are not available. However, many of these preparations are in fact symptomatic therapies, and true antiviral properties via in-vivo experiments and clinical trials remain to be proven.[65,66]

For more on the **African Union Pan African Veterinary Centre** see https://aupanvac.org/

The largest identified gap for therapeutics is the threat of pathogens developing resistance to available drugs (table 2). Research for disease prevention with biosecurity measures, disease monitoring schemes, and early warning or detection systems are required to reduce drug usage and thus mitigate the threat of drug resistance. Both in bacterial and parasitic infections, integrated control approaches must be developed, in which the use of biotechnical, biological, and chemical treatments is combined in a sustainable manner with animal management systems, including pasture management in the case of pasture-borne infections, such as nematodes.

| | Epizootic (including panzootic) | Zoonotic | Enzootic |
|---|---|---|---|
| Target product profile | Drugs to support control strategies | Explore new principles: microbiome manipulation, phage therapy, antimicrobial peptides, and nutritional functional products; new drugs to replace or complement old drugs to which resistance has developed | Explore new principles: microbiome manipulation, phage therapy, antimicrobial peptides, and nutritional functional products; immunostimulants; biological control; and new antibiotics |
| Discovery and understanding | Repurposing of compounds from human medicine | Understand the effects on development of resistant pathogens in humans; chemo-sensitisation of drug resistant pathogens | RNAi silencing; (in vitro) screening programmes |
| Manufacture | NA | New delivery methods | Novel formulations |
| Regulation | NA | International harmonisation of drug quality testing | Drug combinations |

Gaps in the database along the innovation pipeline by disease category. NA=not applicable.

*Table 2:* **Common therapeutic gaps in DISCONTOOLS database**

The mechanisms of development and spread of resistance in bacteria and parasites are, however, different and require specific research. Tools to combat antibiotic resistance are expected to emerge from research into development of alternatives to traditional antibiotics, including new technologies for herd-specific animal vaccines, phage therapy, antimicrobial peptides, nanobodies and egg yolk antibodies (IgY), nanoparticles, immunostimulants, and functional nutritional products.[67–69] The nutritional products are feeds and feed additives that potentially have a positive effect on health beyond basic nutrition, including prebiotics and probiotics.[70] However, novel alternatives that are as effective and affordable as current chemotherapeutics remain elusive.[71] Although most new antibiotics will be reserved for human use, some antibiotics in the pipeline that do not pass safety checks for human application could be repurposed to veterinary applications. Antibiotics that only target animal-specific infections are possible in theory; therefore, research lines on animal-only antibiotics should not be neglected. Research into when and how alternatives work best is needed as well as fundamental research towards bacterial colonisation mechanisms during infection, resistance mechanisms, and the microbiome, which could bring completely new alternatives.

For more on the **International Veterinary Vaccinology Network** see https://www.intvetvaccnet.co.uk/

Parasites are a highly diverse group of pathogens biologically belonging to three groups: arthropods, helminths (both macroparasites), and protozoa (microparasites). The risk of transfer of resistant parasites or resistance genes between animals and humans is generally low. Therefore, combatting resistant parasites is a principal responsibility of the animal health community. Research has identified many different mechanisms used by parasites, even within a single species, to circumvent antiparasitic therapy.[72] Finding the major mechanisms that can underpin diagnostics for resistance and usable novel therapeutic and preventive approaches is challenging.[73] Solutions for resistance to anti-parasiticides require research into new delivery methods and formulations, into chemosensitisation of parasites to increase efficacy and extend the life span of existing anti-parasiticides and drug combinations, and into the international harmonisation of drug quality testing.[74] In addition, there is a need for investment in drug discovery, including evaluation of plant extracts.

## The big five research themes in animal health

New animal disease control tools have a high potential to deliver on great societal challenges, such as public health threats, climate change adaptation and mitigation, and food security. However, to be effective, control tools in isolation are not enough and should be part of an integrated approach in which biosecurity, host–pathogen–environment interactions, contact networks, transmission pathways, prevalence of diseases, and socioeconomic aspects are duly considered. These aspects are included in the STAR-IDAZ research road maps for coordinated international research into animal disease control strategies.[75] Moreover, the 2019 Global Burden of Diseases study has made it clear that an exclusive focus on (human) health-care systems is insufficient to address global health challenges, and that we also need to address deeper societal inequities that are at the root of diseases (appendix p 2).[76] We considered five big research themes that offer a framework for novel and improved animal disease control tools to deliver on the search for a sustainable and healthy planet.

### Vaccinology

Strategies to improve animal health are increasingly focusing on disease prevention, animal resilience, and smart monitoring to facilitate timely interventions. With the apparent re-emergence of epizootic outbreaks such as lumpy skin disease[19] and African swine fever,[77] in Europe and Asia, classical swine fever in Japan,[78] and animal and zoonotic coronavirus infections,[79] vaccination will continue to be a fundamental tool to meet future health challenges. Vaccinology is a very active research area as evidenced by the International Veterinary Vaccinology Network and new technologies (eg, nucleic acid vaccines, peptide vaccines, live viral vector vaccines, and virus-like particles) are leading to unprecedented possibilities for vaccines that induce higher protection, are more stable, or more cost-effective to produce.[59] There are also new developments to improve standardisation and overcome safety and efficacy issues of autogenous vaccines, such as diagnostic approaches predicting the efficacy of autogenous vaccines.[80] New manufacturing processes (platforms) for delivering effective vaccines against emerging (and re-emerging) zoonotic diseases with panzootic potential within a few months after the occurrence of first cases are needed.[81,82] However, development of these technologies will depend on the availability of new antibodies, reagents, and models in target animal species need to be developed.[48] Several promising vaccines (eg, for Bluetongue and Rift Valley fever) are already in development, but require further testing in large-scale trials.[83,84] For vaccines against zoonotic diseases, studies show that a positive public health effect and economic return via vaccination in livestock can happen,[35,85,86] and more studies are needed to support this evidence and bring this concept into practice.

### Antimicrobial resistance

Resistance to antimicrobial medicines has become a global threat to human and animal health.[87] The One Health[88] approach considers an increasingly connected world and emphasises the importance of controlling antimicrobial exposure in all microbial habitats—humans, animals, and the environment alike. The approach also highlights the importance of collaboration across various professions and health sectors. Antimicrobial resistance mitigation efforts rely heavily on safely reducing overall antimicrobial use,[89–91] but despite successful action plans in several countries,[92,93] human, animal, and agricultural antimicrobial use is still increasing globally as of 2022.[87,94] The importance of sustained antimicrobial stewardship strategies in companion animals and livestock is shown by various stewardship policy successes. One example is the EU ban on antimicrobial use for growth promoters since 2006, which led to a measurable reduction of antimicrobial resistance in animals.[95]

There remain many knowledge gaps that must be addressed to support national and global priority setting on antimicrobial resistance mitigation. Successful implementation of action plans remains the biggest challenge.[92] Effective stewardship initiatives must consider the drivers and barriers towards antimicrobial use in livestock and companion animals, which are not fully comprehended. The importance of antimicrobials entering the environment and its contribution to antimicrobial resistance development is poorly understood. Ensuring veterinary bacterial infections remain tractable will require further insights into cross-resistance,[96] and the development of resistance-limiting animal treatment regimens.[97] Holistic solutions will require a much broader approach than the existing focus on reducing antimicrobial use. Indeed, in an environmental sampling study (ie, sewage sites), antimicrobial resistance gene abundance correlated more strongly with socioeconomic, health, and environmental factors than with antimicrobial use.[98] Increased biosecurity and prevention of enzootic animal disease outbreaks should be the basis to reduce the burden of antimicrobial resistance at the human–livestock interface. Antimicrobial use and antimicrobial resistance surveillance is essential to highlight important areas for intervention and provide baselines for progress from mitigation efforts to be assessed against. However, global coordination and standardisation of such surveillance activities is scarce.[99] Advances in genomic sequencing technologies offer the potential to deepen our understanding of human–animal antimicrobial resistance transmission dynamics at various epidemiological scales and across ecological interfaces.[88] Understanding these dynamics at various scales will ensure that the key drivers of resistance transmission can be accurately identified.

## Climate mitigation and adaptation

The changing climate places animal health at risk through increased abundance of disease vectors, altered pathogen survival, and increased livestock disease susceptibility through heat stress, feed, and water shortages. Animal health is a prerequisite to efficient production, which can subsequently reduce greenhouse gas emissions from livestock.[101] The links between diseases, ruminal and gut microbiota, and the microbiome suggest the potential to develop pathogen control strategies and nutritional supplements that reduce greenhouse gas emissions from animal production systems, while simultaneously improving animal health and resilience. Disease control can reduce emissions from animal production systems by enhancing animal production efficiency, and potentially also via direct pathogen–microbiota interactions. In November 2020, scientists warned of a hypothetical positive feedback loop arising from interactions between climate, infectious diseases, and methane emissions, and highlighted the potential of infectious diseases to exacerbate the contribution of livestock to greenhouse gas emissions.[102] Pathogen-induced changes driven by climate change have been estimated to increase methane inputs to the atmosphere by up to 50%;[102] however, more empirical data and rigorous modelling to underpin such estimates are urgently needed.[103]

Making animal health systems resilient to global warming will require climate adaptation measures, which will involve farm management measures, nutritional adaptations, breeding strategies, and protection against new health threats.[104] Better detection and knowledge of heat-induced stress and its impact on immune function and vaccine responsiveness will be a key factor. Heat stress diagnostics, based on animal physiological and behavioural indicators will be needed. Climate change will have direct and indirect effects on the occurrence and distribution of infectious animal diseases by affecting animal behaviour, the immune and endocrine system, feed quality and availability, the distribution of disease vectors and wildlife reservoirs, and pathogen survival outside the host.[105–107] The disease expert panel contributing to DISCONTOOLS judged that 11 (21%) of 53 animal diseases in the database are likely to be affected in terms of spread and impact in response to climate change. These diseases were mostly vector-borne, parasitic, and those passively spread by rodents and flies. For 14 additional diseases, the impact of climate change was considered unknown, whereas for the remainder of diseases, any impact of climate change was considered unlikely. More research is needed to keep infectious diseases tractable under environmental change.

### Bringing prevention into the digital age

The animal health industry is investing in data-driven solutions to provide better insights into livestock and companion animal health. From the livestock perspective in particular, farmers, companies, and governments have the foresight to use big data and artificial intelligence, such as precision livestock farming technologies to manage millions of animals and their health status worldwide.[40] Big data will require both observational and hypothesis driven analysis for their transformation into knowledge and actionable decisions. Open, fair, transparent, and sustainable data platforms are essential for the sharing of data across sectors, countries, and international organisations, and to overcome issues around data ownership, acceptance, and business disruption. Sources of data could be international, For more on **ProMed** see https://promedmail.org

governmental, and non-governmental. Organisations such as ProMed provide rapid, validated, open access, and apolitical datasets on emerging diseases or trends. Placing actionable disease data into the hands of international organisations, such as the World Organisation for Animal Health or EU institutions, will promote the control and containment of emerging outbreaks within an appropriate timeframe. Some existing examples are the established international influenza and classical swine fever databases.[108,109] Such databases include genomic data of pathogens linked to single outbreaks, geocoding, genetic typing, and phylogenetic analysis tools. Accordingly, these databases provide useful tools to trace the source of pathogen introduction and to control disease outbreaks. Providing farmers with actionable animal management information means that they can act rapidly together with veterinarians to safeguard the health of their animals, while achieving optimal production outcomes for a healthy and sustainable food supply. For example, algorithms can be used to monitor live video camera footage and warn free-range poultry farmers when birds should be kept indoors to minimise the risk of introducing avian influenza.[110] Linking genomic, phenotypical, clinical, and diagnostic data streams, might lead to new discoveries in disease prevention and detection, but such data linkage will require huge efforts and continuing improvement of data standardisation, annotation, and sustainable formatting as technologies evolve, as well as consensus building around data ownership, privacy, and access.

## Preparedness

Farmers and competent authorities have for centuries been confronted with severe disease outbreaks that have led to high animal mortality and impacts on agricultural trade and the free movement of animals and people. Factors, such as increasing animal and human populations, increased mobility, and climate change, reinforce the frequency at which these events occur. SARS-CoV-2 has shown the impact of spillover events from animals to humans and vice versa on animal and public health and on the global economy.[111] The COVID-19 pandemic also represents a paramount case to further One Health approaches for managing emerging pathogens that are able to cross the species barrier. A major research focus is the prediction of zoonotic virus reservoirs. An interactive spillover database ranked Lassa virus, SARS-CoV-2, Ebola virus, Seoul virus, Nipah virus, hepatitis E virus, and Marburg virus in the top positions for spillover risk.[112] Rabies virus and the Orthopox viruses, monkeypox, and cowpox viruses, also had a high risk for spillover.[112] Zoonotic spillover risks are related to the viral richness in a host species, host–virus interactions, ecological contact, and phylogenetic distance between the viral host and humans.[114] Deepening our understanding of these factors together with the drivers at the ecological, socioeconomic, and human behavioural levels will be key to prevent future spillover events.[115]

Despite the promise from genomic approaches aimed at developing inventories of pathogens, including the millions of unknown viruses in the wild, the rate, source, and specific causative pathogens of such outbreaks will be difficult to predict.[116] Therefore, preparedness for epizootic outbreaks and for the emergence of new zoonoses should be based on becoming more efficient in the early detection and identification of known pathogens, and emerging infections, followed by risk assessment and the fast development of containment measures. Livestock is a crucial element in such surveillance activities because it acts as the epidemiological link between potential pathogens circulating in wildlife and human emerging pathogens.[117] Containment measures will then include livestock management and preventive modifications of the wildlife–livestock interface.[118] Surveillance strategies based on smart sampling approaches, genomic analysis, artificial intelligence, and sensors have the potential to detect animal health disorders and threats in the food chain before devastating effects occur. Digital and molecular technologies can speed up the back tracing of transmission events and the identification of the source of infection. However, early detection will not only require development of new technologies, but also sustained investment in diagnostic networks and infrastructures, supply chains, capacity building, and international, trans-sectoral coordination. Above all, we must avoid complacency. Response capacity should be built when there is no acute outbreak, and be maintained even in the absence of an obvious threat, to ensure that there is capacity to deliver appropriate responses when disease outbreaks occur. A vigilance mindset will lead to better decision chains, from diagnosis to policy action, and ultimately improve the health of animals, people, and ecosystems.

### Search strategy and selection criteria

We searched the DISCONTOOLS database for each disease separately from March 1, 2020, to Sept 30, 2021. We listed identified gaps in knowledge and control tools for each disease. We noted and classified gaps that occurred for several diseases for each disease group (ie epizootic, enzootic, and zoonotic). We further investigated these gaps with a non-systematic literature search via PubMed, Web of Knowledge, and Google Scholar, using search terms describing the various diseases, pathogens, research developments, and challenges identified in the DISCONTOOLS from Oct 1, 2020 to May 31, 2021.

### Contributors

JC drafted the qualitative database analysis and the initial manuscript. All authors contributed equally to the interpretation of the data, commented on the initial draft, and agreed on the final version of the manuscript.

### Declaration of interests

We declare no competing interests.

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