Shaping the future of vaccination to combat new diseases

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Vaccines have been a cornerstone in the care of animals since the beginning of modern animal production. Following the discovery of the first industrial vaccines against foot and mouth disease in the late 1940s, the number of diseases for which immunisations are available has constantly increased, as has scale and consistency of quality, product efficacy, safety and convenience of vaccine application. As a consequence the overall vaccine market has been one of the fastest growing segments in the industry. This has been driven by technological advances in vaccine development, the emergence of new diseases, changes in husbandry and the continued trend from treatment to prevention.

Today, vaccines represent more than one quarter of the entire global animal health market, with global sales of about $6 billion. Asia accounts for about 20% of the global vaccine market and is growing faster than any other region.

Percentage of biologicals

Vaccine use, particularly in the pig and poultry segments, will outpace traditional therapies as the underlying market trends continue to be very robust. Three primary geo/political factors continually shape the animal health market and drive growth. These factors and additional technological advances will shape the future of vaccination:

- **Overall population growth and urbanisation.**

Population growth and urbanisation, combined with the increase in disposable income in emerging countries, will fuel the demand for more, affordable and safe animal protein. This demand will drive the acceleration of industrialised animal production, and vaccines will be an increasingly important tool for the primary producers.

Considering the cost-benefit of vaccination, the focus for new products will be on reducing the risk of production losses, convenience of product application and ways to improve compliance. Another impact of the urbanisation is the greatly increased risk of disease transmission including zoonotic diseases because of the increased density of human population. This will require increased efforts for control programs including vaccination or hygiene measures.

- **Climate change and globalisation.**

There are a growing number of examples in which climate change has facilitated the movement of vectors carrying certain diseases into new areas. For example, the regular movement north of the Culicoides midge, which carries viruses like Bluetongue or Schmallenberg, has led to the importation of these diseases into Europe, causing significant agricultural losses. Increased global travel and the continued human invasion into rain forest and other natural habitats of new viruses and diseases pose a permanent threat that will continue to bring emerging diseases and new challenges in epidemiology. Examples include Nipah, Hendra, swine and avian flu virus. Vaccines and vaccination programs will be important tools to help control them. This aspect is particularly relevant because many of the diseases have zoonotic potential.

- **Evolving regulatory and political environment.**

The regulatory and political environment is evolving quickly, resulting in ever increasing standards as well as increased importance of animal welfare and food safety. Increased regulatory requirements result in higher standards, costs and time to market. Licensing of next generation products based on GM vaccines of increasing complexity will take longer and cost more. This poses a challenge to regulators and industry to work together and identify new ways of accelerating ways to licence without compromising quality, efficacy and safety in order to be able to meet the challenges of rapidly emerging new pathogens.

In addition, increases in consumer protectionism are driving regulation and legislation to limit the use of antibiotics in animals and increase food safety standards. This poses an opportunity for new, non-antibiotic vaccine technologies, and vaccines are positioned to be an integral part of control programs addressing human food safety pathogens such as salmonella, campylobacter, E. coli O157 and listeria. These organisms typically do not cause disease in their hosts, but do cause serious health problems for people. In fact, public control programs initiated in the UK in the early 1990s showed a reduction in human salmonella cases following vaccination in chickens. This trend will continue in emerging markets and there are early signs of success in Asia.

Meeting market demands

As environmental conditions and market dynamics change, so do the technological solutions. Future vaccines might be combination vaccines made from cutting edge technology, and may even be immunomodulatory therapies that bolster the animal's immune system without directly eliciting an immune response.

Next generation vaccine approaches offer significant innovation to control both existing diseases (overcoming maternal antibodies, extended duration of immunity, multivalent vaccines) and emerging diseases.

The ability to use structural biology to design more efficacious vaccines through the identification of broadly cross-neutralising antibodies, their target epitopes and the ability to synthesise proteins with the appropriate conformation are creating very exciting opportunities for target vaccine design.

These products have the potential to overcome existing paradigms of conventional vaccines such as interference from maternally derived immunity or offering safety and efficacy as opposed to safety or efficacy. Also, next generation vaccine candidates based on such technologies have the potential to adjust more quickly and easily to new circulating strains of a given pathogen. Innovative adjuvants will help to direct and balance the immune response to the antigens in more targeted ways.

Combination vaccines can greatly reduce the cost of animal handling. In fact, there has been a constant increase in the numbers of

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antigens in combinations since the launch of first bivalent vaccine. Today, the combination vaccines have become so complex that the immune system of the animal has become the limiting factor and the risk of interference between the individual valences is high.

Pigs tend to have localized reactions to combination vaccines licensed combinations of more than two antigens are the exception. Poultry vaccine combinations include up to eight antigens, cattle vaccine products include up to 10 or 12 different antigens. Future vaccines will likely include even more combinations. New technologies and a better understanding of the interaction of the antigens with the immune system will keep moving the boundaries.

Better and faster tests

Advances in computer and nanotechnology are continuously driving the cost of gene sequencing and analysis down and allow for faster sequencing of smaller samples. This trend has the potential to change the way we run diagnostics. While today one has to check samples for every pathogen in question, tomorrow we may run a total sequencing of all DNA segments in the sample. Comparing standard databases will give detailed, quick, complete and potentially even quantitative information about any pathogen in the sample.

This will allow a better analysis of each herd's needs and result in more precisely targeted combinations that can avoid stress through avoiding unnecessary valences. 'Lego combos' of vaccine combinations that are customised to the particular needs of a farm are already showing promising results.

Progress in our understanding of pathogens, hosts and their interaction and the increasing ability to gather and analyse large amounts of data in a shorter amount of time will increasingly allow for new products that better address unmet needs.

Today, conventional killed and modified live vaccines offer basic solutions for the key pathogens. Strain evolution and evolving epidemiology will constantly require updating and adjusting these products.

DIVA vaccines

An important need which is only partially met today for controlled diseases like FMD are products that allow for differentiating infected from vaccinated animals (DIVAs). This is important in the context of eradication programs or to prove a disease-free status of a given region or country in the face of ongoing vaccination programs. More DIVA vaccines will allow vaccination as a more widely used tool to combat controlled diseases.

Convenience of vaccine delivery and increased compliance will also help improve the cost-benefit ratio of vaccines. Innovative formulations and in particular devices are increasingly addressing this need. This includes use of needle-free injection systems, spray vaccination, drinking water applications or in-ovo vaccines today. We are seeing promising potential in new technologies such as microneedles or long acting vaccine formulations.

Integrated animal care

While the next generation of recombinant vaccines is already in the research and development departments of the industry, promising new technologies with 'game-changing' potential are already visible on the horizon. Progress in new technologies increases the opportunity for other factors of animal production to potentially complement or even substitute for some of today's use of vaccines.

A better understanding of the factors influencing the early development of the animal's immune system might allow the induction of innate or specific immunity; progress in genetics and cloning might produce animals with resistance to certain diseases. New technologies for biotherapeutics or therapeutic antibodies have the potential to replace antibiotics or achieve the promotion of growth through new mechanisms.

There are significant technical hurdles to overcome and new opportunities give rise to new ethical questions and the need for appropriate risk assessments. Regulatory bodies will need to update and create new regulations to accommodate advances in knowledge and technology before this becomes a viable option.

To address these complex questions, new and much more integrated ways of basic and applied research will have to be defined. As a result, we are already seeing the creation of more complex private-public partnerships with more public funding which will add a new perspective on some of the major unmet needs of the industry.

We are living in a period of profound changes, yet 'futurists' tell us that all indications are that we are only at the beginning of these changes. As a result, the world of animal health vaccines is changing.

Recombinant technology has already made significant advances in the companion animal space and is quickly entering production animals. Next generation vaccines have an ever increasing share of the market and will continue to address unmet customer needs to combat new diseases and to create better combinations and better tailored solutions.

The value share of next generation vaccines today is already high and much of the growth in the segment is driven by new products with specific production benefits. This represents an important contribution of the animal health industry to feed the growing population of our planet and to meet the increasing consumer demands for safe and affordable protein. ■