

Chapter 2

Future Challenges for Vaccinologists

Sunil Thomas, Rima Dilbarova, and Rino Rappuoli

Abstract

Vaccination is one of the cheapest health-care interventions that have saved more lives than any other drugs or therapies. Due to successful immunization programs we rarely hear about some of the common diseases of the early twentieth century including small pox and polio. Vaccination programs have also helped to increase food production notably poultry, cattle, and milk production due to lower incidence of infectious diseases in farm animals. Though vaccination programs have eradicated several diseases and increased the quality of life there are several diseases that have no effective vaccines. Currently there are no vaccines for cancer, neurodegenerative diseases, autoimmune diseases, as well as infectious diseases like tuberculosis, AIDS, and parasitic diseases including malaria. Abuse of antibiotics has resulted in the generation of several antibiotic-resistant bacterial strains; hence there is a need to develop novel vaccines for antibiotic-resistant microorganisms. Changes in climate is another concern for vaccinologists. Climate change could lead to generation of new strains of infectious microorganisms that would require development of novel vaccines. Use of conventional vaccination strategies to develop vaccines has severe limitations; hence innovative strategies are essential in the development of novel and effective vaccines.

Key words Vaccine, Infectious disease, Structure-based vaccine, Antibiotic resistance, Climate change

1 Introduction

Vaccines are one of the greatest achievements of medicine providing protection against debilitating diseases and have spared millions of lives. Smallpox, polio, measles, diphtheria, pertussis, rubella, mumps, and tetanus were once common diseases of man that killed millions of people (until the first half of the twentieth century) before the advent of vaccines. Fortunately, we rarely hear about these diseases today due to the widespread introduction of immunization programs. The introduction of safe, affordable, and effective vaccines has dramatically improved public health, prevented countless hospitalizations, and substantially increased industrial output [1]. Though in the short term vaccines prevent diseases, in the long term mass vaccinations are successful in eradicating infectious diseases. Vaccinations have helped in eradicating several diseases in developed countries; however, there are only

two diseases that have been eradicated globally. Mass awareness programs and aggressive vaccination strategies in the twentieth century were able to control smallpox and in a landmark event the disease was officially declared eradicated in 1980. Rinderpest, a serious disease of cattle, was officially eradicated in 2011, thereby becoming only the second disease to be completely eradicated [1]. Recently the Americas (North and South America) have become the first in the world to be declared free of endemic transmission of rubella, a contagious viral disease that can cause multiple birth defects as well as fetal death when contracted by women during pregnancy. The achievement was due to a 15-year effort that involved widespread administration of the vaccine against measles, mumps, and rubella (MMR) throughout the Western Hemisphere. The declaration of elimination by Pan American Health Organization/World Health Organization (PAHO/WHO) makes rubella and congenital rubella syndrome (CRS) the third and fourth vaccine-preventable diseases to be eliminated from the Americas, following the regional eradication of smallpox in 1971 and the elimination of polio in 1994 (source: World Health Organization). This chapter reviews the future challenges of vaccinologists.

2 Antibiotic Resistance

Though vaccines prevent diseases, there are many infectious diseases without any commercial vaccines available. Hence, antibiotics are prescribed to control these diseases. Unfortunately, abuse/misuse of antibiotics has resulted in generation of antibiotic-resistant bacteria [2]. Abuse of antibiotics is the leading cause of increased morbidity and mortality from drug-resistant microorganisms [3].

Recent studies demonstrated that abuse of antibiotics could lead to several metabolic diseases including obesity, food allergy, and autoimmune diseases [3–5]. Abuse of antibiotics is not restricted to patients alone, but also occurs in the food supply chain. In veterinary medicine antibiotics are used not only in the treatment and prevention of disease but also for growth promotion in food animals [4]; though many countries have banned use of antibiotics for growth promotion there are places where banning is not enforced vigorously. One of the reasons for the incidence of antibiotic-resistant bacteria is due to the uncontrolled use of antibiotics in the food supply chain. Hence there is a need to develop new and improved vaccines for animals so that they are protected during their life-span from different pathogens. Reduced use of antibiotics for the control of diseases in animals will lead to low levels of antibiotics in the food supply chain which could lead to lowering of the incidence of antibiotic resistance.

The Centers for Disease Control and Prevention (CDC) estimates that two million patients suffer from hospital-acquired infections (HAI) (nosocomial infection) every year and nearly 100,000 of them die [5]. HAIs are infections that occur more than 48 h post-admission. HAIs are caused by viral, bacterial, and fungal pathogens. HAIs are caused by viral, bacterial, and fungal pathogens. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, *Pseudomonas aeruginosa*, and vancomycin-resistant *Enterococcus* (VRE) are the major bacteria that cause HAIs. The importance of VRE is that it is capable of genetically transferring its resistance genes to such organisms as MRSA. Vancomycin-resistant MRSA (VR-MRSA) is a major threat, because it is expected to be highly communicable and difficult to treat because of limited antibiotic therapy [5]. As yet there are no successful vaccines for the antibiotic-resistant bacterial strains. Hence there is an urgent need to develop new therapeutic strategies in the control of antibiotic-resistant bacterial infectious diseases.

3 Climate Change and Infectious Diseases

The incidence, outbreak frequency, and distribution of many infectious diseases are generally expected to change as a consequence of climate change. Climate change would affect vector-borne, food-borne, water-borne, and rodent-borne diseases [6].

Temperature and precipitation patterns influence food- and water-borne diseases [7]. Changes in seasonal precipitation and temperature influence vector-borne diseases through (1) effects on vector survival, reproduction rates, habitat suitability, distribution, and abundance; (2) the intensity and temporal pattern of vector activity (biting rates); and (3) rates of pathogen development, survival, and reproduction within vectors [8]. The projected climate changes may shift the distributional ranges of vector-borne diseases. As an example, the number of tick-borne diseases of humans has increased in incidence and geographic range over the past few decades, and there is concern that they will pose an even greater threat to public health in future. Although global warming is often cited as the underlying mechanism favoring the spread of tick-borne diseases, climate will influence which tick species are found in a given geographic region, their population density, the likelihood that they will be infected with microbes pathogenic for humans, and the frequency of tick-human contact [9]. Changes in climate will influence other insect vectors including mosquitoes, fleas, sandflies, tsetse flies, and houseflies, known to carry highly pathogenic microorganisms infecting man.

Due to changes in climate there is concern that ancient bacteria and viruses could revive as global warming melts ice at the poles. Migratory birds and insects could bring the potential

harmful microorganisms to the populated urban/suburban areas. Vaccinologists should be on the lookout for new pathogens emerging in any corner of the planet.

4 Vaccines for Diseases Associated with Urban Areas in the Developing Countries

Rabies is one of the oldest and deadliest zoonotic diseases, killing thousands of people worldwide each year. Rabies is due to viral infection typically transmitted to people via bites from infected animals, especially bats, carnivores, or domestic mammals. The disease has no cure other than vaccination. Because of aggressive vaccination programs for pets, most rabies cases in developed countries are transmitted from wildlife species. However, most rabies in developing countries is canine related, notably stray dogs. The difference between a developed nation and developing nation is how the resources (however small) are managed. Some of the offices in developing countries are occupied by people with no interest in caring the public. The characteristic feature of cities in developing nations is poor urban management. One could observe poor waste management practices—with unmoved garbage at every intersection, stray dogs and cattle sharing the road, open and overflowing drains and sewage, and stagnant water bodies which provide breeding grounds for insects. These unhygienic conditions in cities are favorable grounds for a plethora of infectious diseases. The first line of defense against rabies is controlling the stray dog population. Development of cheaper rabies vaccines for developing countries could lead to better immunization programs in humans and stray animals.

Leptospirosis, a disease caused by the bacteria *Leptospira*, is an emerging public health problem in urban centers of developing countries. The disease is transmitted through infected rodents [10]. 200 serotypes of *Leptospira* have been described [11]. Though vaccines to leptospirosis are available the efficacy is very limited because they usually only protect well against a single serovar. Hence there is a need to develop highly effective vaccines for this disease which could protect against multiple strains of this pathogen.

Other diseases of note that arise from mismanaged urban centers include mosquito-transmitted diseases including malaria, dengue fever [12], and chikungunya [13], and the rodent-transmitted plague. Crowded living conditions and refuse-contaminated flood waters around the shanty towns of Surat, India, provided a breeding ground for rats and infected fleas which were responsible for the 1994 plague caused by the bacteria *Yersinia pestis* [14]. Though targeted vector management can make a difference in terms of reducing vector abundance, once the disease is out of control vaccination is the only strategy to prevent collateral damage to a

population. Currently there are no effective vaccines for malaria, dengue, chikungunya, etc. Vaccinologists should also look out for mutant strains during an epidemic outbreak so as to develop improved and effective vaccines.

5 Vaccines for HIV and Ebola Virus

Acquired immune deficiency syndrome (AIDS) caused by HIV is a serious threat to global public health. Despite intensive research since the 1980s there are no vaccines or drugs that can successfully prevent or eradicate the disease. The major barriers to HIV vaccine development include the variability of HIV, lack of a suitable animal model, lack of correlates of protective immunity, lack of natural protective immune responses against HIV, and the reservoir of infected cells conferred by integration of HIV's genome into the host [1]. Within the main HIV-1 subgroup, Group M, there are nine clades as well as dozens of recombinant forms, and clades can vary up to 42 % at the amino acid level [15]. A vaccine immunogen derived from a particular clade may therefore be ineffective against other clades, posing a significant obstacle to the creation of a global HIV vaccine. Importantly, one of the principal barriers limiting discovery of an HIV vaccine has been that protective immune responses tend to be polyclonal and involve antibodies directed to several different epitopes; thus, antigenic variation among the different HIV-1 isolates has been the major problem in the development of an effective vaccine against AIDS [1]. Although several 3D structures of HIV-1 envelope protein fragments have been determined, this knowledge has not yet led to the design of an HIV-1 vaccine. The mechanism by which an HIV vaccine might confer protection therefore remains uncertain, and an effective vaccine may require induction of an immune response that is significantly different from that seen during natural infection [16]. Overall, current vaccination strategies have not helped in developing a vaccine for HIV; hence novel "out-of-the-box" strategies are essential in developing an HIV vaccine [17].

Ebola virus disease is a severe, often fatal, zoonotic infection caused by a virus of the Filoviridae family. The Ebola virus (EBOV) causes an acute viral syndrome that presents with fever and an ensuing bleeding diathesis that is marked by high mortality in human and nonhuman primates. Fatality rates are higher than other viral diseases with rates of up to 90 % [18]. Ebola viral disease (EVD) affects the poorest people in the African continent. Due to movement of people across borders the disease could rapidly spread and infect any people globally. EBOV spreads through human-to-human transmission via direct contact with the blood, secretions, organs, or other bodily fluids of infected people and with surfaces and materials (e.g., bedding, clothing) contaminated with these

fluids. EBOV glycoprotein (GP1,2) and matrix protein (VP40) are both major components of EBOV. The hemorrhagic disease caused by EBOV is characterized by generalized fluid distribution problems, hypotension, coagulation disorders, and a tendency to bleed, finally resulting in fulminant shock. Vascular instability and dysregulation are hallmarks of the pathogenesis in EBOV hemorrhagic fever (HF). Endothelial disturbances can be caused indirectly, by proinflammatory cytokines such as TNF- α released from EBOV-infected monocytes/macrophages, and directly, following virus infection of endothelial cells. In vitro studies demonstrated that EBOV viral proteins could activate endothelial cells and induce a decrease in blood vessel barrier function [19]. The worldwide challenge posed by the 2014 outbreak of EBOV [20] has underscored the need for effective prevention and treatment options, especially for front-line health care and emergency response workers in the field, and at hospitals and other care facilities. As yet there are no vaccines or therapeutics commercially available to protect against EVD. Hence, there is an urgent need to develop a powerful vaccine which could provide robust protection against the viral pathogen. The EBOV and its high fatality are known since the 1970s. The disease only affects a small percentage of people annually in Africa; hence government agencies as well as International Organizations were not keen to invest in vaccines. If there were vaccines available against EBOV infection, thousands of lives could have been saved in 2014.

6 Development of Powerful Influenza Vaccines

Influenza A viruses are zoonotic pathogens that continuously circulate and change in several animal hosts, including birds, pigs, horses, and humans. The viral pathogen causes infections with various consequences ranging from pandemics to seasonal flu. The emergence of novel virus strains that are capable of causing human epidemics or pandemics is a serious possibility [21]. The World Health Organization estimates that the global disease burden from influenza is around one billion infections, three million to five million cases of severe disease, and between 300,000 and 500,000 deaths annually [22].

Influenza viruses contain 8 single-stranded RNA segments encoding 11 proteins. There are three types of influenza viruses: A, B, and C, with types A and B causing annual human epidemics. A key feature of the influenza virus is its error-prone polymerase, which results in an accumulation of genetic mutations that are selected for in hemagglutinin (HA) and to a lesser extent neuraminidase (NA)—the major surface glycoproteins of the virus. This antigenic drift of the HA protein renews our susceptibility to influenza viruses and is the basis for frequent updating of the

composition of seasonal influenza vaccines. Protection after natural infection is primarily mediated by HA-specific antibodies in serum and mucosa, with the presence of antibodies against NA, conserved influenza proteins, and T-cell responses correlating with reduced disease severity [22].

A novel virus can emerge in humans either through direct interspecies transmission or as a result of molecular exchanges between influenza viruses that already infect humans. Because the influenza virus genome is segmented, coinfection of a single host cell with two or more different influenza viruses can result in a reassortment (or shuffle) of their genetic material. The antigenic shift can lead to a pandemic if the resulting progeny virus contains an HA protein to which humans have no pre-existing immunity, if it has an efficient replication-competent set of internal genes, and if it can readily spread from human to human [22].

Vaccination is the primary strategy for the prevention and control of influenza. Seasonal influenza vaccines are trivalent. Each dose is formulated to contain three viruses (or their HA proteins) representing the influenza A H3N2, influenza A H1N1, and influenza B strains considered to be the most likely to circulate in the upcoming influenza season [22]. Currently, most influenza vaccines are made from virus cultured in eggs, which is a severe production bottleneck during a serious threat of epidemic. There is an urgent need to develop a new efficacious process for influenza vaccine production which could be rapidly and cheaply manufactured [1]. The influenza virus has high mutation rate and a particular influenza vaccine usually confers protection for no more than a few years. Every year WHO predicts the strains of the virus that would be circulating in the following year and the vaccines are manufactured based on these data. The vaccine is formulated each season for a few specific flu strains but does not include all the strains active in the world during that season. A truly universal vaccine that provides lifelong protection against any strain of influenza with one or more vaccinations is certainly a goal that is worth pursuing [22].

7 Development of Vaccines for Viral Hepatitis, Coronavirus, and Norovirus

Viral hepatitis is the most common cause of liver disease and is a major global health problem all over the world. Every year millions of people are infected with the hepatitis viruses. The consequences of chronic disease include cirrhosis, liver failure, and hepatocellular carcinoma. There are six main hepatitis viruses, referred to as types A, B, C, D, E, F, and G. These six types are of greatest concern because of the burden of illness and death they cause and the potential for outbreaks and epidemic spread. In particular, types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and

cancer. The hepatitis B and C are the most frequent reason for liver transplantation. Hepatocellular carcinoma which is one of the ten most common cancers is closely associated with hepatitis B, and may also be associated with hepatitis C virus [23]. As yet there are only vaccines for hepatitis A and B. Hence there is an urgent need to develop vaccines for other hepatitis viruses [24].

Coronaviruses are named for the crown-like spikes on their surface. The viruses primarily infect the upper respiratory and gastrointestinal tract. Coronaviruses probably spread through the air by coughing or sneezing, or by close personal contact. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are novel coronaviruses that cause severe viral pneumonia in humans. The recent appearance of these viruses highlights the continual threat to human health posed by emerging viruses. SARS emerged in the human population in China in 2002, causing a worldwide epidemic with severe morbidity and high mortality rates, particularly in older individuals [25], whereas MERS was reported in Saudi Arabia in 2012. Bats are the natural reservoirs of SARS-like coronaviruses (CoVs) and are likely the reservoir of MERS coronavirus (MERS-CoV). Although a small number of camels have been found to have positive nasal swabs by real-time polymerase chain reaction and to carry antibody against MERS-CoV, the transmission route and the intermediary animal source remain uncertain amongst the sporadic primary cases [26]. All emerging viruses have an animal reservoir, such that the process of viral emergence can usually be categorized as cross-species transmission [27]. Vaccinologists should be aware of the viruses in the animal reservoirs as well as the mutants or recombinants in humans; proteomic and immunological data from both the animal and human mutants could be used to make effective vaccines.

The surge in economies of many developing countries since the last decades of the twentieth century coupled with low-cost airlines and cheap cruises has made air and sea travel affordable, which has led to the increased global movement of people and materials on an unprecedented scale. Outbreaks of noroviruses in cruise ships which can affect hundreds of passengers is an example of the rapid spread of an infectious pathogen; the disease is also known to spread rapidly in semi-closed populations such as hospitals and hotels [1]. These viruses cause gastrointestinal disease, resulting in recurrent bouts of vomiting and diarrhea that typically last 24–48 h. Noroviruses are transmitted via the fecal–oral route, most commonly through infected food or water or person-to-person contact, and result in 267 million infections and over 200,000 deaths each year, mostly in infants and the elderly. Vaccines and therapeutics are under development but face considerable challenges as there is no cell-culture system or small-animal model for human disease, and these viruses are highly heterogeneous and

undergo antigenic variation in response to human herd immunity, further complicating our understanding of the complex immune interactions that regulate susceptibility and disease [28, 29].

8 Development of Vaccines for Tuberculosis and Meningitis

Tuberculosis (TB) (caused by the bacteria *Mycobacterium tuberculosis*) affects the lungs and was declared a global emergency in 1993 by the WHO. More than two decades after this declaration, the disease still remains a serious and considerable threat to global health. TB is spread through air and the disease is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2013, nine million people fell ill with TB and 1.5 million died from the disease. Standard anti-TB drugs have been used for decades, and resistance to the medicines is widespread. Disease strains that are resistant to a single anti-TB drug have been documented in every country surveyed. Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to, at least, isoniazid and rifampicin, the two most powerful, first-line (or standard) anti-TB drugs (source: WHO). The only effective vaccine for TB is the BCG vaccine; however it is effective in children only, not in adults. Hence there is a need for effective vaccines for TB.

Meningococcal meningitis is a form of meningitis caused by the bacterium *Neisseria meningitidis*. Meningitis is characterized by inflammation of the membranes (meninges) around the brain or spinal cord. The bacteria are spread through the exchange of respiratory and throat secretions. For *N. meningitidis*, the amino acid sequence of the protective antigen factor H-binding protein (fHBP) has more than 300 variations. These sequence differences can be classified into three distinct groups of antigenic variants that do not induce cross-protective immunity. Scarselli et al. [30] demonstrated that the structure-based design of multiple immunodominant antigenic surfaces on a single protein scaffold is possible and represents an effective way to create broadly protective vaccines.

9 Development of Vaccines for Arthropod-Borne Bacteria and Viruses

The most important arthropods harming humans include ticks, mites, and mosquitoes. Ticks are responsible for transmission of bacteria of the order Rickettsiales, which include the genus *Ehrlichia* (causes ehrlichiosis in humans and animals and heartwater in cattle), *Rickettsia* (causes Rocky Mountain spotted fever, epidemic typhus, etc.) and *Anaplasma* (causes anaplasmosis), whereas mites are responsible for the transmission of *Orientia* (causes scrub typhus). Lyme disease is caused by the bacterium *Borrelia burgdorferi* and

is transmitted to humans through the bite of infected blacklegged ticks. Tularemia is a disease of animals and humans caused by the bacterium *Francisella tularensis*. As yet there are no commercially available vaccines against any of these pathogens.

Mosquitoes are responsible for the transmission of dengue virus, West Nile virus, chikungunya, yellow fever, Japanese encephalitis, Western equine encephalitis, Eastern equine encephalitis, etc. With the exception of yellow fever there are no vaccines for other mosquito-borne viral diseases.

10 Development of Vaccines for Water-Borne Diseases

A safe, reliable, affordable, and easily accessible water supply is essential for good health. More than a billion people lack access to safe drinking water. Shortage of water leads to people using contaminated water for drinking purposes increasing the risk of water-borne diseases. Water-borne diseases are infections that are transmitted through contact with or consumption of infected water [31]. The predominant members that cause these diseases are protozoans and bacteria. The major protozoans transmitted through contaminated water include *Entamoeba histolytica*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, and *Giardia lamblia*. The major bacteria involved in contaminated water are *E. coli*, *Vibrio cholerae*, *Clostridium botulinum*, *Salmonella*, *Shigella*, and *Campylobacter jejuni*. Vaccines against these pathogens could lead to a decrease in water-borne diseases.

Legionnaires' disease is transmitted by inhalation of aerosolized water or soil contaminated with the Gram-negative bacteria *Legionella pneumophila*. The disease is associated with the bacteria thriving in water coolers, cooling towers, etc. The bacteria cause life-threatening diseases in the urban environment. The bacterium is named after a 1976 outbreak in a Philadelphia hotel. Many American Legions attending a convention in the hotel suffered from the disease and the bacteria was tracked to the cooling tower. A milder infection, also caused by *Legionella* bacteria, is Pontiac fever. As yet there are no vaccines against *Legionella*.

11 Development of Vaccines Against Parasites

The parasites include ectoparasites like ticks, mosquitoes, fleas, and itch mite, and endoparasites including Plasmodium, Entamoeba, Leishmania, Trypanosoma, Babesia, Toxoplasma, Wuchereria, Brugia, Giardia, Ascaris, tapeworm, hookworm, pinworm, whipworm, Onchocerca, Fasciola, and Schistosoma. Most of the diseases are classified under neglected tropical diseases and are the major causes of fatality in poverty-stricken regions of the developing

world. Though the diseases caused by these parasites affect millions of people in the developing world, in the long term (due to climate change, movement of refugees, etc.) they pose a risk to people all over the world. As yet there are no vaccines against these parasites [32]. Hence there is an urgent need to develop vaccines against these parasites causing misery to millions of people.

12 Development of Vaccines for Cancer, Neurodegenerative Diseases, Substance Abuse, and Autoimmune Diseases

Cancer is the leading cause of death in the world. Though there are vaccines for some cancers induced by virus (e.g., cervical cancer) there are no vaccines against large number of cancers. Vaccines that can prevent expression of prostatic acid phosphatase in prostate prevent prostate cancer. Development of cancer vaccines should be a priority as it could reduce the incidence of the disease, thereby reducing emotional and economic hardship to millions of people.

As people live longer they are more prone to neurodegenerative diseases like Alzheimer's and Parkinson's diseases. As yet there are no cures for these diseases. A vaccine to prevent this disease will decrease the enormous burden on society.

The currently available medications for the treatment of drug abuse have had only limited success. Anti-addiction vaccines, aimed at eliciting antibodies that block the pharmacological effects of drugs, have great potential for treating drug abuse [33].

As yet there are no vaccines for arthritis, type I diabetes, allergy, multiple sclerosis, and other autoimmune diseases. A vaccine for these diseases could improve the quality of life of people suffering from these debilitating diseases.

13 Development of Vaccines for Fishes, Poultry, and Farm Animals

In intensive culture or farming, where single or multiple species are reared at high densities infectious disease agents are easily transmitted between individuals. Pathogens are easily transported through water and this helps in the quick spread of disease in fishes and other species of aquaculture. Effective vaccination strategies lead to reduced antibiotics in aquaculture [34]. Hence vaccines provide the best strategy to control infectious diseases in fishes.

The highly pathogenic avian influenza virus H5N1, which was limited to poultry, spread to migratory birds and poses a major challenge to animal and human health. Since pandemic influenza virus has its origins in avian influenza viruses, H5N1 virus has to be considered a potentially serious pandemic threat. New influenza virus pandemics in the twenty-first century are a certainty. It has

been reported that H5N1 viruses are taking a huge toll on the poultry industry in many developing countries, and this directly or indirectly impacts both economic and social well-being. While the H5N1 virus transmits zoonotically from infected poultry to humans, often with fatal consequences, such transmission remains inefficient [35]. Though there are vaccines for H5N1 in poultry, the vaccines are not commercially available for humans. It will be a challenge to vaccinologists to develop a vaccine for multiple strains of avian influenza.

As yet there are no vaccines for many infectious diseases affecting farm animals. Heartwater, a rickettsial disease of ruminants, caused by *Ehrlichia ruminantium* is one of the most important diseases of livestock in Africa. This tick-borne illness can significantly decrease productivity in regions where it is endemic. As yet there are no vaccines for this disease. Similarly, Johne's disease (JD) is a chronic disease affecting ruminants and other species caused by the pathogenic *Mycobacterium avium* subsp. paratuberculosis (MAP). This fastidious bacterium infects and survives in the intestines; MAP-infected cattle can remain asymptomatic for years while transmitting the pathogen via fecal contamination and milk. MAP is able to survive the process of pasteurization as well as chemical processes seen in irrigation purification systems. Subsequently meat, dairy products, and water serve as key vehicles in the transmission of MAP infection to humans. Recent studies demonstrate that MAP is associated with Crohn's disease (CD) in humans [36]. A novel vaccine against MAP could decrease the incidence of MAP in cows and cattle, thereby preventing its occurrence in the food supply chain.

Viruses such as coronaviruses also cause a range of diseases in farm animals and domesticated pets, some of which can be serious and are a threat to the farming industry. Economically significant coronaviruses of farm animals include porcine coronavirus and bovine coronavirus, both of which contribute to diarrhea in young animals. Development of vaccines against these viruses will be beneficial to the agriculture industry.

14 One Health Initiative and Vaccines

The number of pathogens known to infect humans is increasing with time. It is not understood whether such increase reflects improved surveillance and detection or actual emergence of novel pathogens. On average, three to four new pathogen species are detected in the human population every year. Most of these emerging pathogens originate from nonhuman animal species [37]. Zoonotic pathogens (pathogens transmissible from animals to humans) represent approximately 60 % of all known pathogens able to infect humans and 70 % of all emerging infectious diseases [38, 39].

Their occurrence in humans relies on the human-animal interface, defined as the continuum of contacts between humans and animals, their environments, or their products [37]. Certain zoonotic diseases have the potential for pandemic spread by human contagion, such as avian influenza, SARS, and the Middle East respiratory syndrome coronavirus, and others for regional cross-border epizootics, such as yellow fever, Venezuelan equine encephalitis, and Rift Valley fever [39]. Animals, including livestock and companion animals, also suffer illness and death following infection with many zoonotic infections, and livestock and poultry are subject to large-scale intentional destruction as a means of preventing human infections, resulting in huge economic losses.

A collaborative effort encompassing multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and our environment will be beneficial and is the basis of the concept of the One Health initiative. The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals, and the environment. The synergism achieved will advance health care for the twenty-first century and beyond by accelerating biomedical research discoveries, enhancing public health efficacy, expeditiously expanding the scientific knowledge base, and improving medical education and clinical care. The complexity, timeline, and cost of development of animal vaccines and the regulatory hurdles for product approval are far less than for human vaccines. Thus interventions based on the immunization of animals could lead to rapid and relatively inexpensive advances in public health [39].

15 Future Strategies for the Development of Vaccines

Edward Jenner, Louis Pasteur, and Maurice Hilleman developed vaccines by isolating, inactivating, and injecting infectious agents. The vaccines developed by these technologies saved millions of people and many of those vaccines are still in use today. Influenza, oral and inactivated polio, measles, mumps, and rubella are good examples of the vaccines that we still use and were developed with this empirical approach. Since the 1980s new technologies started to emerge that made possible vaccines that were impossible with the empirical approach. The first technology was recombinant DNA that made vaccinologists possible to express the hepatitis B virus-like particle (VLP) in yeast and produce large amounts of vaccines. More recently recombinant DNA technologies were used to generate yeast or baculovirus strains expressing VLPs containing the L1 protein of papillomavirus. The next technology that changed the vaccine landscape was the conjugation technology. In this technology, capsular polysaccharides purified from *Haemophilus*

influenzae, 13 serogroups of pneumococcus or meningococcus A, C, Y, and W, covalently linked to carrier proteins have been licensed during the last 25 years and have completely eliminated the diseases caused by these bacteria. Finally, the advent of genomics allowed the use of the entire genome of pathogens and to search for protective antigens that were difficult or impossible to identify with conventional technologies. The prototype vaccine developed by genome-based approach, also known as reverse vaccinology, is the vaccine against *Meningococcus B* that was licensed in Europe in 2013 and the USA in January 2015 [40].

Many new technologies are emerging that are likely to dramatically change the world of vaccines. These include new powerful adjuvants, the ability to design immunogens using their crystal structure (structural vaccinology), and the ability to make synthetic vaccines (using different classes of RNA, peptides, carbohydrates, etc.) [41].

References

1. Thomas S, Luxon BA (2013) Vaccines based on structure-based design provide protection against infectious diseases. *Expert Rev Vaccines* 12:1301–1311
2. Furuya EY, Lowy FD (2006) Antimicrobial-resistant bacteria in the community setting. *Nat Rev Microbiol* 4:36–45
3. Porco TC, Gao D, Scott JC, Shim E, Enanoria WT et al (2012) When does overuse of antibiotics become a tragedy of the commons? *PLoS One* 7(12), e46505
4. Phillips I, Casewell M, Cox T et al (2004) Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J Antimicrob Chemother* 53:28–52
5. Reed D, Kemmerly SA (2009) Infection control and prevention: a review of hospital-acquired infections and the economic implications. *Ochsner J* 9:27–31
6. Semenza JC, Herbst S, Rechenburg A, Suk JE, Höser C et al (2012) Climate change impact assessment of food- and waterborne diseases. *Crit Rev Environ Sci Technol* 42:857–890
7. Semenza JC, Suk JE, Estevez V, Ebi KL, Lindgren E (2012) Mapping climate change vulnerabilities to infectious diseases in Europe. *Environ Health Perspect* 120:385–392
8. Semenza JC, Menne B (2009) Climate change and infectious diseases in Europe. *Lancet Infect Dis* 9:365–375
9. Estrada-Peña A, de la Fuente J (2014) The ecology of ticks and epidemiology of tick-borne viral diseases. *Antiviral Res* 108:104–128
10. Levett PN (2001) Leptospirosis. *Clin Microbiol Rev* 14:296–326
11. Wang Z, Jin L, Wegrzyn A (2007) Leptospirosis vaccines. *Microb Cell Fact* 6:39
12. Quintero J, Brochero H, Manrique-Saide P, Barrera-Pérez M et al (2014) Ecological, biological and social dimensions of dengue vector breeding in five urban settings of Latin America: a multi-country study. *BMC Infect Dis* 14:38
13. Nagpal BN, Saxena R, Srivastava A, Singh N, Ghosh SK et al (2012) Retrospective study of chikungunya outbreak in urban areas of India. *Indian J Med Res* 135:351–358
14. Clem A, Galwankar S (2005) Plague: a decade since the 1994 outbreaks in India. *J Assoc Physicians India* 53:457–464
15. Hemelaar J (2012) The origin and diversity of the HIV-1 pandemic. *Trends Mol Med* 18:182–192
16. Johnston M, Fauci A (2011) HIV vaccine development—improving on natural immunity. *N Engl J Med* 365:873–875
17. Cohen YZ, Dolin R (2013) Novel HIV vaccine strategies: overview and perspective. *Ther Adv Vaccines* 1:99–112
18. Hoenen T, Groseth A, Feldmann H (2012) Current ebola vaccines. *Expert Opin Biol Ther* 12:859–872
19. Wahl-Jensen VM, Afanasieva TA, Seebach J, Ströher U et al (2005) Effects of Ebola virus glycoproteins on endothelial cell activation and barrier function. *J Virol* 79: 10442–10450
20. Weyer J, Grobbelaar A, Blumberg L (2015) Ebola virus disease: history, epidemiology and outbreaks. *Curr Infect Dis Rep* 17:480

21. Medina RA, García-Sastre A (2011) Influenza A viruses: new research developments. *Nat Rev Microbiol* 9:590–603
22. Lambert LC, Fauci AS (2010) Influenza vaccines for the future. *N Engl J Med* 363:2036–2044
23. Zukerman AJ (1996) Hepatitis viruses. In: Baron S (ed) *Medical microbiology*, 4th edn. Chapter 70.
24. Law LMJ, Landi A, Magee WC, Tyrrell DL, Houghton M (2013) Progress towards a hepatitis C virus vaccine. *Emerg Microb Infect* 2, e79
25. Weiss SR, Leibowitz JL (2011) Coronavirus pathogenesis. *Adv Virus Res* 81:85–164
26. Hui DS, Memish ZA, Zumla A (2014) Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. *Curr Opin Pulm Med* 20:233–241
27. Cleaveland S, Laurenson MK, Taylor LH (2001) Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. *Philos Trans R Soc Lond B Biol Sci* 356:991–999
28. Koo HL, Ajami N, Atmar RL, DuPont HL (2010) Noroviruses: the leading cause of gastroenteritis worldwide. *Discov Med* 10:61–70
29. Debbink K, Lindesmith LC, Donaldson EF, Baric RS (2012) Norovirus immunity and the great escape. *PLoS Pathog* 8(10), e1002921
30. Scarselli M, Aricò B, Brunelli B, Savino S, Di Marcello F et al (2011) Rational design of a meningococcal antigen inducing broad protective immunity. *Sci Transl Med* 3:91ra62
31. Hunter PR, MacDonald AM, Carter RC (2010) Water supply and health. *PLoS Med* 7(11), e1000361
32. Bethony JM, Cole RN, Guo X, Kamhawi S et al (2011) Vaccines to combat the neglected tropical diseases. *Immunol Rev* 239:237–270
33. Shen XY, Orson FM, Kosten TR (2012) Vaccines against drug abuse. *Clin Pharmacol Ther* 91:60–70
34. Sommerset I, Krossøy B, Biering E, Frost P (2005) Vaccines for fish in aquaculture. *Expert Rev Vaccines* 4:89–101
35. Peiris JS, de Jong MD, Guan Y (2007) Avian influenza virus (H5N1): a threat to human health. *Clin Microbiol Rev* 20:243–267
36. Ghadiali AH, Strother M, Naser SA, Manning EJ, Sreevatsan S (2004) *Mycobacterium avium* subsp. paratuberculosis strains isolated from Crohn's disease patients and animal species exhibit similar polymorphic locus patterns. *J Clin Microbiol* 42:5345–5348
37. Gortazar C, Reperant LA, Kuiken T, de la Fuente J, Boadella M et al (2014) Crossing the interspecies barrier: opening the door to zoonotic pathogens. *PLoS Pathog* 10(6), e1004129
38. Taylor LH, Latham SM, Woolhouse ME (2001) Risk factors for human disease emergence. *Philos Trans R Soc Lond B Biol Sci* 356:983–989
39. Monath TP (2013) Vaccines against diseases transmitted from animals to humans: a one health paradigm. *Vaccine* 31:5321–5338
40. Giuliani MM, Adu-Bobie J, Comanducci M, Aricò B et al (2006) A universal vaccine for serogroup B meningococcus. *Proc Natl Acad Sci USA* 103:10834–10839
41. Rappuoli R, Pizza M, Del Giudice G, De Gregorio E (2014) Vaccines, new opportunities for a new society. *Proc Natl Acad Sci U S A* 111:12288–12293

Vaccine Design

Methods and Protocols: Volume 1: Vaccines for Human
Diseases

Thomas, S. (Ed.)

2016, XIX, 873 p. 131 illus., 89 illus. in color., Hardcover

ISBN: 978-1-4939-3385-3

A product of Humana Press