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The interface of animal and human vaccines

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Editorial overview

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The historical legacy of zoonotic viral diseases includes more than 50 million human deaths (3% of the world's population) due to the appearance of a novel influenza virus in the early 1900s as well as the emergence of previously unknown diseases such as hantavirus pulmonary syndrome in 1993 [1] and severe acute respiratory syndrome (SARS) in 2003 [2]. Preventing epidemics resulting from other emerging viral diseases, whether due to ordinary interactions of humans and animals, to man-made environmental changes, or even to increased exposure following natural disasters such as earthquakes or tsunamis, depends on the harmonization of all aspects of animal and human health. This recognition of the inextricable interplay between animal and human diseases led to the development of the 'one health' concept, which aims to foster synergistic relationships that promote the wellbeing of both animals and humans [3].

Vaccination is generally a very effective way to control the spread of viruses among and between animals and humans. Although for some viruses such as hantaviruses, which are carried by persistently infected rodents, it would be very difficult to prevent human infections by vaccinating the natural host, for other viruses, interrupting the infection of animals could prevent human disease. One of the best-studied examples of this strategy is rabies vaccination of animals. As described by Briggs, great strides in controlling wild-life rabies have been made since the advent of new generations of rabies vaccines including recombinant vector-based vaccines. Despite this accomplishment, and despite the existence of vaccines that are 100% effective in preventing human disease, more than 50,000 people worldwide die from rabies each year, most of whom contracted infections from dogs. As the author indicates, a coordinated approach including epidemiological studies, pre-exposure vaccination of humans and dogs in addition to the established post-exposure vaccination regimens is crucial for preventing these human deaths, and she suggests that this effort could be enhanced by including a contraceptive in the vaccines to reduce dog populations in areas where rabies is prevalent.

Another example of vaccinating animals to prevent human disease is described by Bird and Nichol for Rift Valley fever virus (RVFV) in Africa. RVFV is transmitted from infected livestock, such as cattle and sheep, to humans by mosquito bite or by contact with infected animal tissues. Disease in humans is generally self-limiting although a small percentage of people develop hemorrhagic fever or acute retinitis leading to blindness. Drought resistant mosquito eggs can harbor the virus for long periods of time, and when heavy rainfall occurs, mosquitoes carrying RVFV flourish, resulting in a new epidemic cycle of RVF in susceptible animals, with eventual spillover to humans [4]. With the development of reverse genetics systems for

producing live-attenuated RVFV vaccines, it is now possible to tailor vaccines for maximum efficacy without reversion to virulence. These modern vaccines, along with mosquito control measures, offer the promise of eliminating the explosive outbreaks of disease associated with this virus that have occurred in the past.

Fausther-Bovendo, Mulangu and Sullivan address issues associated with vaccination against another hemorrhagic fever virus, Ebola virus (EBOV), which causes disease in humans and non-human primates in Africa. The authors detail the complexities of developing a vaccine against a very high consequence pathogen of uncertain etiology that appears only sporadically. Evidence points toward bats as a natural reservoir of EBOV, but efforts are still underway to confirm and define the host and virus associations. Even with such information, it would be highly impractical to attempt vaccinating bats to prevent infection of humans and nonhuman primates because so little is known about the life cycles of the many different species of bats in EBOV endemic regions. Thus, the most likely targets of an EBOV vaccine are at risk laboratory workers and individuals in areas where an epidemic is occurring. In addition, because EBOV and related filoviruses are considered to be biological warfare or bioterrorism threats, efforts have been made to develop a vaccine that could be stockpiled for use in such events. An another vaccine target population is endangered great apes, which appear to be as susceptible to EBOV disease as humans. To date, several vaccine candidates against EBOV have shown promise in laboratory studies, although none have yet progressed toward licensure. As licensure will depend on studies conducted under the Food and Drug Administration's 'Animal Rule' which is described in the paper by Burns, reliable animal models must also be developed.

Eradication of viral diseases through vaccination has been the ultimate quest of virologists since smallpox was declared to no longer exist in nature in 1980 [5,6]. Enthusiasm for similar victories has dampened since then, as it has proven to be extremely difficult to eradicate most viral diseases, even those such as poliovirus, which like smallpox virus, is an exclusive human pathogen. Remarkably, the second virus to be eradicated after smallpox was a veterinary pathogen, rinderpest virus, a devastating disease of cattle that has indirectly affected human health by causing famines. This example offers hope and important lessons to be learned for similar successes with related human viruses such as the closely related measles virus. De Swart, Duprex and Osterhaus describe the successful eradication of rinderpest virus (RPV) in 2011 and investigate parallels and differences to the situation around eradication of measles virus. Both viruses are highly species restricted; thus, strategies similar to those used against RPV might also be useful for measles eradication. The authors point out, however, that eradication of RPV was enabled by the availability of a temperature-stable, live-attenuated vaccine, and the ability to stop mass vaccination to track remaining pockets of viral infection, which were then eliminated by targeted vaccination and culling of animals. The measles vaccine currently used still requires a cold chain and general mass vaccination will have to be maintained until the virus is eradicated in all parts of the world due to the danger of re-introducing the virus into naïve populations by international travel. The authors further discuss the possibility that one of the many viruses similar to RPV already present in animals, such as canine distemper virus, could evolve to jump species and fill the niche vacated by RPV.

The emergence of animal viruses as human pathogens in the wake of eradication is further discussed by Reynolds, Carroll and Karem, who compares facets of human monkeypox to smallpox. Because vaccination of humans against smallpox also prevented them from developing monkeypox, the eradication of smallpox along with cessation of smallpox vaccinations has resulted in the appearance of monkeypox in susceptible humans. As she describes, however, there are several natural barriers for monkeypox to become widespread in humans without significant evolutionary changes that would increase human-to-human transmission.

In addition to emergence of animal viruses to fill ecological niches vacated by eradicated human pathogens, it is also possible for viruses to emerge due to species jumping events. Such events have become increasingly apparent as new tools for identifying novel viruses in wildlife have been developed. Delwart describes the potential for using these new molecular methods for biosurveillance and detection of new viruses and discusses the evidence for cross-species transmission events for a number of viral families. Such studies underline the importance of continuous surveillance and coordination of animal and human health efforts as is the goal of the one health initiative. Many previously unknown viruses have been identified including new viruses infecting humans; however, studies to correlate these viruses with specific clinical manifestations largely remain to be conducted. Nevertheless, knowledge of their existence is likely to speed any future efforts at vaccine development in the event that a pathogenic link is discovered.

A final and important interface between animal and human vaccines is the use of animal models for licensure of human vaccines for which it is impossible or unethical to use humans for efficacy testing. Burns describes regulatory aspects of the U.S. Food and Drug Administration (FDA) rule, 212 CFR 601.90, commonly known as the 'Animal Rule' which allows for the use of animal data to support efficacy claims of a human vaccine. Because animal models that reflect human disease are a requisite

for licensure under this rule, great efforts are being made to develop suitable animal models, especially nonhuman primate models for a variety of diseases.

One animal model that shows promise for animal rule studies with a number of viruses is the common marmoset, as described by Carrion and Patterson. These small new world primates are said to be especially appropriate for high containment studies both because of space constraints within those laboratories, and also because they have an immune system similar to that of humans. As the authors discuss, marmosets have now been tested as models for hemorrhagic fever viruses requiring biosafety level 4 containment, such as the arenaviruses Lassa and Junin viruses, and the filoviruses EBOV and Marburg virus. Marmoset models have also been developed for the respiratory disease caused by SARS-coronavirus, and for encephalitis caused by infection with eastern equine encephalitis virus (EEEV).

Development of larger nonhuman primate models for EEEV as well as Venezuelan (VEEV), and western equine encephalitis viruses are discussed by Dupuy and Reed. Most studies to date have used either rhesus or cynomolgus macaques as models for disease that occurs after aerosol exposure to these viruses. Although the infectious dose in these models is relatively high and more studies on pathophysiology will be needed, the macaque models for these three alphaviruses hold much promise given that the clinical symptoms closely resemble human disease and neutralizing antibody titers could be used as a correlate of protection. All three of these alphaviruses are considered to be biowarfare agents, and evidence exists for the past weaponization of VEEV by several countries [7]. For biodefense, a vaccine that would prevent disease after aerosol exposure to virus is required, but developing an animal model mimicking a human disease resulting from an unnatural exposure route is especially challenging and relies mostly on observations from the less than 200 laboratory infections with VEEV that resulted in two deaths [8].

Conclusions

Viral zoonoses are an important cause of human morbidity and mortality. As more information has accumulated, it has become obvious that animal health and human health cannot be separated. Animals not only function to maintain and amplify pathogenic viruses in nature, but cross-species transmission can occur for members of numerous viral families and such events have in the past, and likely will continue in the future, to give rise to new veterinary or human disease agents. Vaccination of wildlife or domesticated animals can be effective for preventing some viral diseases of humans, but not all. Vector or host control measures are often also required, and for certain viruses, it is simply not feasible to vaccinate the wide variety of hosts that harbor them in nature. Likewise, eradication of zoonotic viruses through vaccination, while a worthy goal, will be possible for only a few viruses and will depend on an ability to completely control the disease through mass vaccinations. The possibility that the biological niche of an eradicated virus will be filled by another pathogen must also be considered. The development of modern vaccines is costly and obtaining efficacy data for some agents may prove to be impossible due to limited case numbers. Economic aid and alternative licensure paths will likely be required to provide vaccines for many viral pathogens. Finally, animals are now playing another important role in vaccine development efforts by serving as efficacy models that will provide data that potentially can be used to license safe and effective human vaccines. The one health concept for humans and animals is clearly here to stay.

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