VETERINARY VIROLOGY

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Summary

Veterinary virology and prion research has contributed greatly to our understanding of viruses and prions, the infections and diseases that they cause and their epidemiology and ecology. The importance of veterinary virology and prion research to animal health and the quality of our food supply is obvious and widely appreciated. However, the contributions of veterinary virology and prion research are not limited to animal health and the quality of our food supply. Veterinary virology and prion research has also had several major direct impacts in our understanding of human diseases. For example, many important human viruses or prions (or agents very closely related to them) were discovered by veterinarians, veterinary virologists, or prion researchers. Most human viruses and prions originate from animal agents that cross the so-called “species barrier” and became infectious to human beings. Research in animal viruses is therefore directly related to emerging human diseases. Veterinary virology and prion research has also led to many developments that directly impact human health.

For example, both traditional and modern rational vaccines were developed, or heavily influenced, by veterinary research. Veterinary viruses have also been used as surrogates of human viruses in the discovery and development of novel antiviral drugs and vaccines against human pathogens. Moreover, pathogenesis of human viral infections is also often studied by analyzing that of closely related veterinary viruses. In this article,

we will discuss these less appreciated direct roles of veterinary virology and prion research in human health and well-being.

1. Introduction

In this article, we will revisit the importance of veterinary viruses and veterinary virology to human health and well-being. We will also include the prions, which together with viruses are the smallest transmissible infectious agents and were consequently studied together with viruses until very recently. Veterinary virology is of course of paramount importance to animal health, which is in turn essential for the safety of our food supply. The viruses that infect any of the animal species used as major sources of protein in the human diet can all threaten human health and well-being. There is a low but concrete probability of viral pandemics in any of these animal species, which would have drastic impacts on the supply of proteins for the human diet. The latest outbreak of food and mouth disease virus (FMDV) in the UK in 2001 is a good example of a geographically restricted but major disruption to the production of animal protein. In only 10 months, 581,802 heads of cattle (approximately 1 in 20), 3,487,014 of sheep (approximately 1 in 10), and 146,145 pigs in the UK were lost to the outbreak. Veterinary virology is therefore directly pertinent to the security of the food supply, importance which is obvious and widely recognized. However, veterinary virology also has direct impacts in human health, impacts which are not so often equally well appreciated.

Viruses and prions pose a major direct threat to global human health. Many viruses affecting humans are actually zoonotic, that is they infect animals and are maintained in animal reservoirs from which they spread to human beings. Old human viruses such as influenza are continuously re-entering into the human population from their animal reservoirs, with a low but concrete probability of producing another global pandemic. Such threat was just highlighted by the 2009 H1N1 strain, which most likely was recombined in pigs before being transmitted to humans. Other more recently identified viruses, such as hepatitis E (HEV), are most likely periodically transmitted to humans directly from their animal reservoirs. New human viruses or prions such as SARS, Nipah, or bovine spongiform encephalopathy (BSE, also known as "mad cow disease") also periodically enter into the human population from animal reservoirs. It is currently accepted in Public Health that *"most new human infections are of animal origin."* Before they enter into human populations, most viruses are therefore perpetuated in susceptible animals. Major outbreaks of animal disease can also provide a large source for the introduction of novel viral pathogens in the human population. For example, the large outbreak of BSE eventually resulted in the introduction of a new prion disease to humans, variant Creutzfeldt-Jakob disease (vCJD). Veterinary virology is consequently directly pertinent to emerging and established infectious human diseases.

Several animal viruses are also closely related to human viruses, being transmitted by similar routes, producing similar diseases, and being controlled by similar immune responses. Such animal viruses are therefore excellent models to study pathogenesis of, and therapeutic and preventive approaches against, the equivalent human viruses. This approach has been especially useful in the development of novel vaccines. It has also been useful to understand the pathogenesis of, and even developing drugs against, human viruses that infect no practical animal models, such as HCV or HIV. Veterinary virology is therefore also directly pertinent to our understanding of human disease, and to the development and testing of novel antiviral therapeutics or vaccines.

As the importance of veterinary virology and prion research for animal health is widely appreciated, we will focus this article in the discussion of selected examples that illustrate some of the many, but less appreciated, direct impacts of veterinary virology and prion research in human health.

2. Veterinary Sciences in the Foundations of Virology and in Ongoing Virus Discovery

Viral diseases constitute a continuous threat to human health. Viruses such as influenza continue to produce periodic epidemics and kill scores of human beings. Influenza is estimated to kill more than 36,000 people per year in the USA and 500,000 in the world. The flu pandemic of 1918 is estimated to have killed up to 1 in 20 people living at the time. The recent emergency of a novel H1N1 strain proves that new pandemics are likely to occur in the not so distant future. Viral diarrheas are one of the major causes of infant death in large parts of the world. They are estimated to cause 5 to 20 million infant deaths in Africa and Latin America per year. HIV has already killed more than 25 million people and it currently infects more than 33 million more (23 million of them in Sub-Saharan Africa). Hepatitis C virus (HCV) infects 3 to 4 million more people every year, resulting in 170 million infected people in the world and an estimated 1.7 million cases of liver cancer. New viral diseases are constantly threatening to enter into the human population and produce serious pandemics. Virology research is therefore essential to human health.

Veterinary sciences have played major roles in virology research since the very origins of the discipline. The search for novel infectious agents started immediately after the seminal works by Pasteur, Koch and their contemporaries had established the bases for the microbial theory of infectious diseases. A purely technical development, the Chamberland-Pasteur unglazed porcelain (ultra)filter, resulted in the discovery that some infectious agents were much too small to be regular bacteria. Bacteria, parasites or fungi could be identified under the optic microscope, but infectivity was then the only property that allowed the identification and characterization other infectious agents. The infectivity of infectious agents of animals and plants could be readily tested, in contrast to that of human agents. In those early days, therefore, much progress was made on veterinary (and plant) viruses.

Tobacco mosaic virus, TMV, was the first infectious agent identified to be ultra-filterable, by Ivanofsky and Beijerinck (Mayer had earlier shown that the disease could be transmitted by the “juice” of ground leaves of infected plants). However, these studies failed to consider the agent as a novel microorganism. Ivanofsky focused on potential technical aspects of ultracentrifugation, which he assumed had allowed bacteria to pass through the filter. Beijerinck instead did realize that the filterable agent was distinct from bacteria, but he considered the infectivity being in an infectious fluid (from which the name “virus” -poison- was derived). For such reasons, many refer to a virus of cattle, food and mouth disease virus (FMDV), as the first to be discovered. Like Ivanofsky and Beijerinck had found before for TMV, Loeffler and Frosch (in collaboration with Koch) found the agent of FMDV to be ultra-filterable. But Loeffler and Frosch recognized the infection to be transmitted by a novel type of particulate agent much smaller than bacteria. FMDV is therefore often considered as the first virus to be identified. FMDV was without discussion the first mammalian virus identified, and the first virus shown to produce a known infectious disease in organisms other than plants.

Veterinary virology kept on playing a leading role in early virology. While many veterinarian viruses were being discovered, the first human virus, yellow fever virus, was identified only in 1901 and the second one, in 1907. At the end of the first decade after the discovery of FMDV, 13 animal and only 3 human viruses had been identified. Veterinary virology also took the lead in identifying many of the virus families that include the agents of important human diseases. The rabbit myxomavirus was the first poxvirus identified (in 1898), 22 years before human poxviruses were even observed. Likewise, the swine pseudorabies virus (PRV) was the first herpesvirus identified (1902), 17 years before the first human herpesvirus (herpes simplex type 1). Animal virology also identified the first picornavirus (FMDV), tumor virus, solid tumor virus, influenzavirus, alphavirus, papillomavirus, parvovirus, encephalitis virus, arenavirus, calicivirus and coronavirus, among others. For the first 60 years of virology, there was in fact no discrimination between veterinary and human virology. Such lack of discrimination was in not small part responsible for the explosive growth in virology knowledge during those yearly years.

Even after the early years, veterinary virology has continued playing major roles in the discovery of viruses that infect humans. In more recent years, the focus has been on the identification of emerging human viruses. Perhaps the most dramatic example is the discovery of Hendra virus as the causative agent of an outbreak that killed 14 horses and their trainer in Australia in 1994 (and half of all other human beings infected since then). A related virus, Nipah, caused a first outbreak in Malaysia in 1998-99, which killed 105 of the 265 people infected. Nipah has continued causing repeated outbreaks ever since, mostly in India and Bangladesh, with a mortality rate of approximately 75%. The latest outbreak was in 2007, but others will likely occur.

Hendra virus was discovered by veterinary virologists at the Animal Health Laboratory of CSIRO Livestock (Australia) as the causative agent of an outbreak of respiratory illness that affected an entire stable and killed 14 racing horses (and their trainer). Following on this work, Nipah was promptly identified as so closely related to Hendra that both viruses are commonly considered together. The group at the Animal Health Laboratory identified the ability of these viruses to infect a variety of domestic and laboratory animals and their routes of secretion. Most importantly from a human health perspective, they further progressed to identify fruit bats (“flying foxes” of the genus *Pteropus*) as natural reservoirs for these viruses, and horses and pigs as intermediate reservoirs in close proximity to humans. The more recent identification of the mechanisms whereby these viruses enter intro cells may eventually result in the development of novel antiviral strategies to prevent infection with such viruses.

The veterinary virologists at the Animal Health Laboratory of CSIRO Livestock have even more recently developed a potential vaccine that protects against these two pathogens. The vaccine showed solid protection of cats against lethal Nipah challenge. Therefore, veterinary virology was critical in identifying these two new human viruses. It was also critical in characterizing their ecology, thus helping to prevent further human infections, and in developing protective measures against infection with these viruses. Veterinary virology therefore continues to play a major role in the identification and characterization of novel viral pathogens that affect human beings.

Novel viruses are constantly introduced into the human population from their animal reservoirs, as recently shown by SARS and in the more distant past by Junin virus and HIV. In most cases, socio-ecological changes are the most likely cause of the exposure of humans to these new viruses. Deforestation, human settling in remote areas (often to enjoy an “undisturbed” landscape), ecotourism, increases in human population in countries with large previously uninhabited areas, a taste for exotic foods, and climate changes resulting in movement or displacement of wild animals to areas in closer contact with human beings, are all factors contributing to our current enhanced exposure to animal viruses. International travel for business, tourism, or to visit relatives leaving in different countries, is a major factor helping to promptly disseminate any new virus through the world. As none of these factors are likely to drastically change in the near future, our exposure to novel viral pathogens will continue to be exacerbated for the foreseeable future. It is estimated that approximately three quarters of all newly discovered human viruses come from animal reservoirs. Continuous research in veterinary virology is therefore essential to ensure that the required expertise will be available when the next animal virus is introduced into the human population.

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Biographical Sketch

Luis M Schang was born in Argentina, where he studied Veterinary Sciences. He earned a Medico Veterinario degree at the Universidad de Buenos Aires in 1987. He then completed doctoral studies at the University of Nebraska-Lincoln (Lincoln, NE, USA), studying porcine and bovine herpesviruses. He obtained a Ph.D. in molecular virology in 1996. He then pursued post-doctoral studies at the University of Pennsylvania (Philadelphia, PA, USA) from 1997 to 2000.

While still an undergraduate student, he was an undergraduate Teaching Assistant at the Departments of Biophysics and then Biochemistry of the Universidad de Buenos Aires. He then did an internship at the Instituto Nacional de Tecnologia Agropecuaria (INTA), in Castelar (Argentina). He was briefly a Research Associated at the University of Nebraska-Lincoln, and became an Assistant Professor in the University of Alberta (Edmonton, AB, Canada) in 2001. He was promoted to Associate Professor in 2006. Dr. Schang's research is focused on studying the requirement for cellular factors in replication and pathogenesis of viruses and prions, with an ultimate goal of identifying novel antiviral strategies. He was one of the earliest proponents of developing antiviral drugs targeting viral proteins, an approach that is now considered mainstream. He is currently studying the possibility of developing antiviral drugs targeting the lipid envelope of virions.

Dr. Schang is an active member of the International Society for Antiviral Research, and the International Society for Nucleosides, Nucleotides and Nucleic Acids. He is also a member of PrioNet Canada.