Global Impact of Animal Research on Infectious Diseases: A CDC Perspective

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I am going to discuss the global impact that animal research has had on infectious disease, with a CDC angle. I will provide a historical perspective, but primarily focus on the science and the key scientific contributions that have made an impact on prevention of infectious diseases globally. I have selected several infectious diseases for which there is visible progress and clear and specific examples of accomplishments due to animal research. Some of my discussion will involve regulations and policy as well as CDC-specific work.

Obviously, not everything is about infectious diseases and a few key accomplishments that are noninfectious disease-related are shown in Box 1, denoting the years and recognition with the Nobel Prize. Some of those accomplishments are making it possible for people to live their lives to the fullest today.

The work on animals started many years ago but it continues to be amazing. When it comes to infectious diseases, a very specific and major accomplishment based on animal research is the development of vaccines, and it is hard to point to a vaccine that has not been “touched by an animal” in some way. Six of those diseases are shown in Box 2.

Every year, 2½ million children worldwide do not die because their infections and death are prevented by vaccines. Unfortunately, the same number of children still die from vaccine-preventable diseases—over a period of 10 years, that is 25 million children. Each life is precious. We frequently hear about individual tragedies of five or ten people being killed in an accident; now imagine almost 7,000 children a day dying—or not dying because of the contributions that were available through animal research.

There are many other areas in the infectious disease world—from pathogenesis studies to mechanisms of immunity, testing of new antimicrobials, and development of monoclonal antibodies—that have been recognized as major accomplishments. In all of these studies animals have not necessarily always been visible, but they are the unsung heroes. Charles McCarthy told a compelling story about Pepper, the Dalmatian...
CDC’s animal care and use program is an exemplary one. Animal care and use programs, one of them ACUPO, to make especially over the past decade in developing policies and AAALAC and its leadership for helping us and guiding us. Care and Use Program Office (ACUPO). CDC is grateful to established in 1985. Several years ago, we established our Animal AAALAC since 1966 and we had our first IACUC estab­lished to control malaria because it was an important disease globally that was killing American soldiers, and be­cause of numerous military posts in the Southeast of the United States where malaria was indigenous. Hence, we started as a malaria agency and our first work with animals involved killing mosquitoes. CDC has been accredited by AAALAC since 1966 and we had our first IACUC established in 1985. Several years ago, we established our Animal Care and Use Program Office (ACUPO). CDC is grateful to AAALAC and its leadership for helping us and guiding us especially over the past decade in developing policies and animal care and use programs, one of them ACUPO, to make CDC’s animal care and use program an exemplary one.

CDC has about 200 active protocols and 200 principal inves­tigators at four physical locations in Atlanta, Lawrenceville, Morgantown, and Fort Collins. Three key areas of research are infectious diseases, reagent production for the detection of infectious diseases, and a smaller emphasis on environ­mental health including nanotechnology. We have three IACUCs.

One of the things that resulted from the work with AAALAC is the structure that shows how critically important oversight of animal care and use is at the agency. The three key components of CDC’s animal care and use pro­gram are the IACUCs, the Animal Care and Use Program, and the veterinary and animal support staff. All of this con­verges toward the CDC Institutional Official (IO), and I have had the honor of serving as CDC IO since 2004.

There are 88 species of animals in use at CDC (including field studies), very similar to the kinds of animals that NIH is using in its research. Ferrets are extremely popular at CDC in influenza transmission studies as they have a lot of com­monalities with humans, including similar host receptors for the influenza viruses and very similar disease progression. The CDC’s research on animals is a reflection of our broad area of research in infectious disease globally.

I want to share what it is that the research on animals globally and at CDC has done for the global community. I will focus on five diseases—HIV/AIDS, influenza, hepatitis, rabies, and malaria—and demonstrate some of the key scientific accomplishments over the past few decades. I have separated, in some way, contributions made by others and the key CDC contributions in certain areas. These are not my personal picks and choices; I have consulted with colleagues who work in these areas. I do apologize in advance if this becomes excessively scientific, but I am primarily a scientist and then an IO, and I thought that sprinkling in some heavy science would not hurt.

I will start with influenza. Even without the H1N1 infl uenza, between 3,000 and 49,000 people die every year of illnesses in the United States associated with complications of seasonal influenza (Thompson et al. 2010). Information collected on a weekly basis by CDC on circulating influenza strains and trends in influenza illness are key activities. Major contributions of research on animals for influenza were in the development of antivirals; specifically, neuraminidase (NA) inhibitors, which we know as oseltamivir (Relenza) and oseltamivir (Tamiflu), drugs that inhibit NA activities. NA is an enzyme that allows propagation of the virus in the upper respiratory tract and the movement of the progeny virus, from an infected cell (von Itzstein 2007). Those have been extremely potent and valuable drugs. Safety and efficacy testing on these drugs has been done on animals, making them really much better for people, putting them into clinical trials at the point when much is already known.

Specific CDC contributions fall into several areas. One had a lot of attention a couple years ago and that was the reconstruction and characterization of the 1918 pandemic virus (Tumpey et al. 2005). Work with the reconstructed

| Box 1 Selected discoveries related to noninfectious diseases and conditions |
|-----------------------------|-----------------|
| 1921 Insulin* (dog, fish)   | 1929 Vitamins supporting nerve growth* (chicken) |
| 1942 Rh factor (monkey)     | 1943 Vitamin K* (rat, dog, chicken, mouse)       |
| 1956 Open heart surgery and cardiac pacemakers (dog) | 1964 Regulation of cholesterol (rat) |
| 2002 Mechanisms of cell death* (worm) |

* Nobel Prize awarded for the research

| Box 2 Selected discoveries related to infectious diseases |
|-----------------------------|-----------------|
| (a) Development of vaccines |
| 1796 Smallpox (cow)         | 1881 Anthrax (sheep) |
| 1885 Rabies (dog, rabbit)   | 1933 Tetanus (horse) |
| 1934 Polio* (mouse, monkey) | 1968 Rubella (monkey) |

* Nobel Prize awarded for the research

(b) Work recognized by the Nobel Prize
| 1905 Pathogenesis of tuberculosis (guinea pig, horse, rabbit) |
| 1928 Pathogenesis of typhus (guinea pig, rat, mouse) |
| 1945 Penicillin tested (mouse) |
| 1984 Monoclonal antibodies developed (monkey) |
| 1997 Prions discovered (hamster, mouse) |

Sources: www.amprogress.org, www.fbresearch.org

who was stolen, sold, and resold; that event prompted an un­believable outcry in the public domain and demands for Congress to act. Congress did act and since 1966 a number of subsequent policies, acts, and regulations have been put in place to protect the animals that are so vital for our research.

CDC history goes back to 1946 when the agency was established to control malaria because it was an important disease globally that was killing American soldiers, and be­cause of numerous military posts in the Southeast of the United States where malaria was indigenous. Hence, we started as a malaria agency and our first work with animals involved killing mosquitoes. CDC has been accredited by AAALAC since 1966 and we had our first IACUC established in 1985. Several years ago, we established our Animal Care and Use Program Office (ACUPO). CDC is grateful to AAALAC and its leadership for helping us and guiding us especially over the past decade in developing policies and animal care and use programs, one of them ACUPO, to make CDC’s animal care and use program an exemplary one.
1918 virus was conducted at and supported by CDC. The USDA, NIH, and the Armed Forces Institute of Pathology (AFIP) all provided support for many other aspects of this research. One can inquire as to why it is important to know what the virus of 1918 looked like. It is because we would like to see what it is that made it so deadly, and we would like to see whether those components, in its genetic makeup, can be found in new and emerging viruses. This was one of the most fundamental contributions of our agency in influenza research.

In terms of vaccines, we continuously evaluate influenza strains that come in from all over the world and assist in selection of the vaccine candidates. We also do a great deal of preclinical evaluation and then participate in evaluation of novel vaccine candidates and drugs. Our key scientist in this area is Dr. Terry Tumpey, who is also a member of our IACUC. Obviously, we want to get the most prominent CDC researchers to serve on the IACUC. Ten years ago we had a difficult time with that, but with AAALAC support and overall agency support, scientists now consider it an honor to serve on our IACUC.

The second disease I want to focus on is HIV/AIDS. The number of people affected is staggering. In spite of so many years of dealing with it we do not have a vaccine. There is a lot of research going on, and a vaccine would be the most important prevention measure. However, there are a lot of other efforts that scientists are undertaking that I will share. There are over 33 million people living with HIV today. That is living with HIV, not having a death sentence with HIV. Every day, more than 1,000 children are newly infected with HIV worldwide. Two million people die of AIDS every year. As can be the case with other infectious diseases, the distribution of disease burden is not equal in the world and thus it is usually those in the developing world who are most affected. The prevalence in Africa is unbelievable—there are countries where over 30% of child-bearing women are infected.

The contributions in terms of animal research when it comes to HIV/AIDS have been from very basic research in understanding the pathogenesis as to why it is so challenging to develop a vaccine and other prevention measures. Unlike for polio, one cannot say in a simple sentence, “The ultimate outcome of research was the development of a vaccine.” But one can certainly say that there has been so much progress with regard to anti-HIV medication that people can live longer and fuller lives with HIV these days.

Several contributions are considered critical. Work on nonhuman primates and monkeys has allowed for a better understanding of phylogenetic relationships among different HIV viruses and simian retroviruses, which has made it possible to develop simian models to advance HIV research using simian immunodeficiency virus (SIV). Many consider this one of the most fundamental contributions of animal research (Daniel et al. 1985; Letvin et al. 1983). Another major contribution has been development and refinement of a macaque monkey model, known as the repeated low-dose (RLD) model. This model has had a profound impact on HIV prevention research, especially with regard to antiretroviral preexposure prophylaxis medications that are now considered to be a potentially important way to help people prevent HIV infection. Clinical trials are looking at different means and routes (e.g., oral or vaginal) of delivering antiretroviral preexposure prophylaxis medications to the site of initial HIV infection. These studies have immensely benefited by the development and results obtained from the RLD model and the initial work using macaque monkeys.

What CDC does cover, in its own way and within its spectrum, includes a broad array of activities: from core work, such as model development, pharmacodynamic and pharmacokinetic studies, all the way to drug resistance and virus susceptibility studies. In addition, novel interventions and devices including pills, gels, cervical rings, and the like are being explored that have promise for preventing HIV infection in people.

The third disease I am focusing on is viral hepatitis. Again, it has an unbelievable global burden: 350 million people live with the hepatitis B virus (HBV) as a chronic infection, and 170 million are chronically infected with hepatitis C. In the United States, there are about 3,000 documented, reported cases of hepatitis A, which translates to about 25,000 cases a year because reported and actual cases are not necessarily the same, depending on the kind of surveillance available (e.g., how reliable the reporting is). But there was a dramatic decline in the number of cases following the introduction of the hepatitis A vaccine. For acute hepatitis B there are about 4,000 new cases every year, with an estimated 38,000 in 2008. There was a decline in the number of cases after the introduction of the vaccines.

A key contribution to the discovery of the HBV vaccine, the main component being the HBV surface antigen, comes from the use of chimpanzees for vaccine efficacy studies. Most of the work for hepatitis is done on chimpanzees, and that is the only infectious disease for which research at CDC is conducted on chimpanzees. A study by McAleer and colleagues (1984), more than a quarter-century old, is the first example of a vaccine produced from recombinant cells that is effective against human viral infection. The CDC also contributed to the discovery of hepatitis C virus via its pioneering work on infectivity studies done on chimpanzees (Choo et al. 1989). One of the things we realized several years ago is that there comes a time when one must decide whether and how much to focus on the research on chimpanzees. We have narrowly limited this research and moved all six chimpanzees from the CDC campuses to New Iberia in Louisiana. We consider that a major accomplishment because we felt that in terms of social settings life would be much better for them there.

Rabies is a disease that is frequently forgotten because we do not hear about it often and we do not think about dying from it. However, it occurs in more than 150 countries worldwide and over 50,000 people die every year, many of them children. Every year, 15 million people get rabies post-exposure prophylaxis. Unfortunately, once a person has been exposed, without such prophylaxis there is only one way to
go: to die. Postexposure prophylaxis is extremely important and it is again the animal work that has enabled us to understand its value. It is fascinating to think that something we still consider a major contribution when it comes to animal research for rabies goes back 60 years (Koprowski et al. 1950). Postexposure prophylaxis using a guinea pig and hamster model set the stage for the recommendations we use today (i.e., to use the serum and a vaccine), and this is what the Advisory Committee on Immunization Practices at CDC still recommends. This major contribution saves an extraordinary number of lives.

One CDC contribution that I am very proud of is that the research on animals can be helpful to the animals even though it is primarily intended for humans. Specifically, that is the development of an oral vaccine for animals against rabies, the first experimental use of oral vaccination (Baer et al. 1971). In Western Europe and the United States there is a substantial decrease in the number of cases among animals. Why is this important? It is important because this shows that we can prevent an infection in animals without slaughtering them. When I talk to my colleagues who study rabies—every September there is a global conference on rabies at CDC—they say that the pictures showing how cruelly animals are treated in some parts of the world because of prevention of rabies are just too horrible to see. To have a vaccine that saves animals’ lives and prevents drastic measures is an unbelievable success, in addition to the 15 million people that receive prophylaxis whose lives are also saved, thanks to the laboratory animals.

And the last disease that I will briefly mention is malaria. Today, 3 billion people in the world live in areas where they are susceptible to malaria transmission—in over 100 countries—and it is estimated that about 1 million people die every year from malaria. Most of those deaths occur in Africa. Malaria is the fifth leading cause of death from infectious disease in the world and the second in Africa. Cases in the United States are, as a rule, imported. Key contributions of animal research for malaria go fairly far back; they are in the development of drugs against malaria (Davidson et al. 1976). Understanding the pathogenesis of malaria through the use of animal models facilitates work on the development of vaccines and other preventive measures. A nonhuman primate model using monkey malaria was key in this study for developing the drugs active against relapsing forms of malaria, which is a major problem for malaria prevention and control. A key CDC contribution has been the development of many different models in monkeys for testing of different types of vaccines and drugs against Plasmodium falciparum and P. vivax. Models using monkey malaria parasites have also been developed that can serve as substitutes for various drug and vaccine studies where human malaria parasites and New World monkey hosts are not available (Collins et al. 2006).

I would like to end with a couple of general comments. If there is one thing to take from this talk, it is that there are hundreds of millions of people whose lives have been affected in a positive way from research where animals are critical. At the same time, animals used in research do not volunteer and do not give their consent, and we should be immensely thankful and appreciative of the sacrifices they make. We have to be just as grateful to those of you who have devoted your entire careers to animal welfare. There’s an old saying that it’s not what you do, it’s how you make people feel while you’re doing it. Recollections of such colleagues about their own experiences exemplified why their efforts were successful. It was because they made scientists feel good and ethical knowing that their research can not only be done but done with dignity and respect for the animal.

It was an honor to be a part of this conference with all of you and those who made it possible for all these accomplishments to take place and for millions of lives to be saved.

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References