Is There Variation Among Vaccine Recipients? A Response To Questions From Dario Ringach And The Relevance Of This Discussion For Claims Regarding Animal Models

Ray Greek MD

The story so far

In a blog titled Chimpanzees, Science, and Ethics, I stated: "As readers of this blog know, small differences between members of the same species can result in dramatic differences to perturbations such as vaccines and other drugs." I almost did not write that essay as I thought the points self-evident and uncontroversial. One reason I eventually did write the essay was to once again point out that there is a difference between ethics and science and that one can discuss one without the other. I anticipated feedback regarding that aspect of the essay but did not anticipate the rest of the feedback I received, some of which is quoted below.

Dr Dario Ringach posted (the posts quoted below can be found at the above link):

> If individual differences among members of the same species is critical to establish the reaction to a vaccine, how do you explain the successful development of vaccines for polio, diphtheria, tetanus, pertussis, measles, rubella, influenza, and so on? You seem to be a step shy from arguing that parents should not vaccinate their kids. Is AFMA anti-vaccination?!

Later Dr Ringach posted:

> If this [RG's statement about variation in vaccine response] was true in general then vaccinations would have been impossible to develop. Furthermore, if we accept the general validity of the statement, it logically follows you must oppose the use of vaccinations. I then asked if you and AFMA are opposed to vaccinations.

And:

> I merely pointed out that if you believe in your own statement that "small differences between members of the same species can result in dramatic differences to perturbations such as vaccines" then you and AFMA should recommend parents to avoid vaccines. If not, explain why not and how that squares with your statement.

Then:

> On one hand you acknowledge that vaccines work. On the other hand, you state that in general small differences can have "dramatic" consequences for how humans respond to vaccines. An attack on your logic suddenly becomes an attack on you.

And finally:

> The reduction in Hib incidence after the vaccine was licensed was 98.6%, reduction in measles was 99.95%, in mumps 99.6%, for whooping cough 97.6%, polio 99.99%, rubella 99.7%... All these decreases are correlated with the introduction of the vaccine.
> Here are the data: http://www.hhs.gov/nvpo/concepts/intro6.htm
> So please, explain how this is consistent with the "dramatic" effects we expect from one individual to the next.

I was reluctant to respond to the above for reasons I will list and attempted to end the discussion with this:

> To begin with, Dr Ringach is presenting a false dichotomy. But even assuming we got beyond that, the answer to his question lies in an understanding of the prediction position Shanks and I explain in *Animal Models in Light of Evolution* and even in FAQs About the Use of Animals in Science. So, here's the deal. IF Dr Ringach (or LifeScientist or anyone else interested in this) will explain the essence of my prediction argument (something I do not think he can do hence I see no reason to go into why vaccination per se works despite the fact some people respond to some vaccines when others do not), hint: it involves those statistics I harp on, THEN I will take the time to once again explain how you can have dramatic differences while simultaneously saying that a practice, for example vaccination, is on the whole effective etc. AND I will contrast and compare the logic and science of those facts with using animal models per se to predict drug and disease response in humans.

As can be ascertained from the above, the answers to all of Dr Ringach's questions can be found in our book *Animal Models in Light of Evolution* [1] and or in our articles [2-4] and my previous blogs.

I *am* writing this essay however, as it gives me the chance to once again make more or less the same points I have made elsewhere and to make those points with a slightly

different background—vaccines. This essay should establish, per Dr Ringach's comments, the following:
1. There is variation, sometimes dramatic, in vaccine response.
2. The reasons for this variation are the same as what we have been saying about variation to drug response in general. Specifically, that small differences in genetic make-up can result in dramatic differences in response to perturbations to the complex systems known as humans and animals. (Variation also exists secondary for reasons that are not gene-based, for example differences in vaccine preparation, exposure to UV light, and environmental factors. But the questions this essay are concerned with revolve around the gene-based differences, hence I will focus on them.)
3. The reason vaccines *per se* can be said to be a success while animal models *per se* cannot be considered successful for predicting human response to drugs and diseases lies in the statistical evaluation of the practice and a theory that allows us to put that data in an appropriate context.
4. This discussion is yet another example of the disingenuousness, or perhaps ignorance, of the vivisection activist.

It is also important to note what this essay is *not* about. I am not addressing trans-species extrapolation or applying vaccine research in animals to humans. I have addressed the fundamentals of trans-species extrapolation in numerous other places. So I will try here to avoid the arguments that I usually make, since this topic is somewhat different from my standard fare.

Variation

Some of Dr Ringach's criticisms above fall under the fallacy called a *false dichotomy*. A false dichotomy is when someone presents two options as either/or options when in fact they are both correct together. Either option would be correct in what it affirms but not in what it denies. For example the question: "Are zebras' black or white?" The answer, of course is "Both," but the question makes it appear that they can only be one or the other. Or, a false dichotomy may be present because other options exist besides those given. For example two options are presented but there are, in reality, 10 options. In this case, the false dichotomy is that vaccines are not either 100% effective or 100% ineffective. In reality the response varies. They *do not* either work or not work. Even the infectious diseases that vaccines prevent affect different people differently. Ovsyannikova et al.:

> Clinical studies demonstrate that vaccine response is far more complex than a simple binary categorization of success and failure. Clinicians and public health officials frequently focus primarily on vaccine delivery as the critical aspect of successful vaccination. The implication is that if a child receives a vaccination, that child will have responded to that vaccine. However, the paradox that vaccine-preventable diseases occur among highly vaccinated populations suggests that a more sophisticated understanding is required [5]. [6]

On the other hand, people, uneducated in science or infectious diseases, could make a *prima fascia* case that vaccines are in fact 100% effective. After all, society has eliminated small pox and has the real possibility of eradicating polio. The ability to

control infectious diseases, through sanitation, vaccines, and antibiotics represents arguably the most important and cost effective advances in increasing lifespan and quality of life. [7-9] Given the unqualified success of vaccines in general, the question has been posed: does this response invalidate the position of Shanks, Greek, and Greek regarding the importance of interspecies and intraspecies variation? Vaccination in general has relied on the one-size-fits-all approach and has worked well with diseases like smallpox being eradicated and other diseases decreasing in frequency to be almost unheard of in developed societies where vaccination is a near universal phenomenon. But science is about looking deeper and that is exactly what I will do in this essay.

It has been known for some time that immunizations offer different degrees of protection and that side effects vary. Vaccines are not 100% effective in all patient populations. It has been long appreciated that certain vaccines were risky in the immunocompromised patient population. Ovsyannikova et al.:

> While delivery of vaccines remains the foremost challenge with current vaccines, understanding of the variation among individuals with regard to antibody formation may not only address the variation of protection observed among recipients [6], but may also provide a key to the next generation of vaccine development. [10]

Kimman et al. state:

> Vaccines induce a variable response and therefore have a variable protective efficacy. Some vaccinated individuals even do not respond at all to particular vaccinations. These differences are partly determined by environmental factors, such as the presence of maternal antibodies, nutrition, in particular vitamin A deficiency, or environmental infections, and partly by the genetic background of the vaccine recipients, which is the focus of this review paper. *Genetic differences in vaccine-induced immune responses are easily explained by the polymorphic nature of immune response genes, which are more polymorphic than other gene families. Comparing sequences of genes common to rodents and humans for example revealed that proteins involved in host defense have diverged both within and between species 3 times as quickly as other proteins* [11].
>
> The extent of varying response and nonresponse to vaccination has been most extensively documented for measles and hepatitis B virus vaccination. Primary vaccine failure occurs in 2-10% of the vaccinated individuals following measles vaccination and in 5-20% following hepatitis B vaccination. These data are assessed by postvaccination antibody [immunoglobulin (Ig)] testing, but cases of measles have also been documented to occur in properly immunized persons. Vaccine failure clearly depends on the specific vaccine, as it occurs only rarely after tetanus toxoid vaccination. [12] (Emphasis added. Brackets in original.)

Children and infants typically respond differently than adults to vaccines and infectious diseases in general. Joseph Albietz a pediatric intensivist from the University of Colorado

wrote the following in a blog on Science-Based Medicine titled Why Universal Hepatitis B Vaccination Isn't Quite Universal:

> As the name suggests, infection causes damage primarily to the liver, though the spectrum of disease experienced by any one person can be quite broad. In adults, 50-70% of infections are asymptomatic or mild enough to not come to medical attention. The remaining adults experience a range of hepatitis lasting weeks to months, with ~1% of these being a fulminant, life-threatening infection. Adults are relatively efficient in their ability to clear the virus after the initial infection, and only ~10% become chronicly [sic] infected carriers.
>
> Children, on the other hand, present a very different pattern of disease. Though ~90% of infected children are initially asymptomatic, they are rarely able to clear the virus. 90% of infants and 25-50% of those 1-5 years old will become lifelong carriers.
>
> HBV is a relatively stable virus posing a serious public health threat with humans as the only known reservoir, and as such is a prime target for prevention, and theoretically eradication, through vaccination. The first vaccine against HBV became available in 1981, and the current recombinant vaccine has been in use since 1986. As a recombinant vaccine it contains proteins normally made by HBV, but does not have the virus itself, and therefore carries no risk of HBV infection.
>
> As far as efficacy is concerned, the HBV vaccine has a very high response rate, inducing an appropriate antibody response in more than 95% of people from birth to 30 years of age, and decreasing but still significant response rates in older age groups. Immunity from the vaccine lasts at least 20 years in healthy individuals.

Genetic variability to the HBV vaccine has been described, but much work remains. [13] [14] Genetic variation in infants has been described for vaccines for polio, pertussis, and tetanus [15] as well as to other vaccines. [16, 17] [18] [19]

Lambkin et al. state:

> What is the genetic basis to allow a micro-organism to invade and kill one person while his neighbor escapes unharmed? . . . The clinical effectiveness of influenza virus vaccination is dependent on several vaccine-related factors, including the quantity of hemagglutinin within the vaccine, the number of doses administered, and the route of immunization. In addition, the immunocompetence of the recipient, their previous exposure to influenza virus and influenza virus vaccines, and the closeness of the match between the vaccine and circulating influenza virus strains, all influence the serologic response to vaccination.
>
> However, even when these vaccines are administered to young fit adults a proportion of individuals do not mount a significant serologic response to the

> vaccine. It is not clear whether these nonresponding individuals are genetically pre-programmed to be nonresponders or whether failure to respond to the vaccine is a random event. There is good evidence that nonresponsiveness to hepatitis B vaccine, another purified protein vaccine, is at least partially modulated by an individual's human leucocyte antigen (HLA) alleles. Because CD4+ T cells, which control the neutralizing antibody response to influenza virus, recognize antigens in association with HLA class II molecules, we recently conducted a small study to investigate whether there was any association between HLA class II molecules and nonresponsiveness to influenza virus vaccination. This work revealed that the HLA-DRB1*0701 allele was over represented among persons who fail to mount a neutralizing antibody response. This preliminary finding is important because it potentially identifies a group who may not be protected by current vaccination strategies. Further investigation into the role of HLA polymorphisms and nonresponse to influenza virus vaccination, and vaccination against viruses in general, is clearly required. [20]

Crislip in Science-Based Medicine blog titled Flu Vaccine efficacy from Oct 9, 2009:

> Second, response to the vaccine is not 100%. The older and more immunoincompetent are the least likely to develop a good antibody response to the vaccine. In a bit of medical irony, the more likely a patient is to need protection from the vaccine, the less likely they are to get a protective antibody response from the vaccine.

Clements et al. (via Crislip):

> The efficacy of live attenuated cold-adapted (ca) reassortant influenza A H3N2 and H1N1 virus vaccines against experimental challenge with homologous wild-type virus 7 months after vaccination was compared with that of licensed inactivated virus vaccine in 106 seronegative (hemagglutination-inhibiting antibody titer less than or equal to 1:8) college students. The live attenuated virus vaccines induced as much resistance against illness as did the inactivated vaccine. Vaccine efficacy, measured by reduction in febrile or systemic illness in vaccines, compared with that in controls was 100% for ca H3N2 vaccine, 84% for inactivated H3N2 vaccine, 79% for ca H1N1 vaccine, and 67% for inactivated H1N1 vaccine. Less protection was conferred against upper respiratory tract illness; there was 50 and 77% protection in ca and inactivated H3N2 vaccines, respectively, but there was no protection in ca or inactivated H1N1 vaccinees. The duration, but not the magnitude, of H1N1 wild-type virus shedding in both ca and inactivated vaccinees was significantly reduced compared with controls. In contrast, a significant reduction in the duration and magnitude of H3N2 virus shedding was observed in ca vaccinees but not in inactivated vaccines. After wild-type virus challenge, live ca virus vaccinees demonstrated resistance at least as great 7 months postvaccination as did inactivated virus vaccinees. [21]

Crislip:

> The NEJM this month had a nice study on the relative efficacy of killed vrs attenuated vaccine in a healthy adult population that was allowed to get seasonal flu naturally. The end point was culture or positive PCR.

Crislip then quotes Monto et al. from the *New England Journal of Medicine*:

> A total of 1952 subjects were enrolled and received study vaccines in the fall of 2007. Influenza activity occurred from January through April 2008, with the circulation of influenza types A (H3N2) (about 90%) and B (about 9%). Absolute efficacy against both types of influenza, as measured by isolating the virus in culture, identifying it on real-time polymerase-chain-reaction assay, or both, was 68% (95% confidence interval [CI], 46 to 81) for the inactivated vaccine and 36% (95% CI, 0 to 59) for the live attenuated vaccine. In terms of relative efficacy, there was a 50% (95% CI, 20 to 69) reduction in laboratory-confirmed influenza among subjects who received inactivated vaccine as compared with those given live attenuated vaccine. The absolute efficacy against the influenza A virus was 72% (95% CI, 49 to 84) for the inactivated vaccine and 29% (95% CI, -14 to 55) for the live attenuated vaccine, with a relative efficacy of 60% (95% CI, 33 to 77) for the inactivated vaccine. [22]

Crislip:

> Perfect? No. 72% protection from the inactivated vaccine. Not bad. Other studies have demonstrated the live attenuated vaccine efficacy rates of 50% or better.

(Crislip cites [23] in support of the 50% figure.)

Crislip:

> No vaccine is perfect, and the measles vaccine is no different. Measles vaccine is about 90-97% effective in preventing infection, depending on the population studied. Or to think of it another way, 3 to 10% of the population would remain susceptible to the disease even if we had 100% of the population vaccinated.

3-10% unprotected is a dramatic difference.

The vaccine for small pox is one of the medical success stories of the 20th century. But side effects from the smallpox vaccine may be life threatening and include dilated cardiomyopathy, generalized vaccinia, myocarditis and or pericarditis, and post-vaccinial encephalitis. [24-26] Furthermore, the vaccine is contraindicated in a significant percentage of the population. [27] This has led to a search for a new vaccine. [28] Duke-Cohan et al.:

> We further demonstrate that the humoral immune response to vaccinia among different individuals is not uniform in specificity or strength, as different IMV and

> EEV targets predominate within the group of immunogenic proteins. This heterogeneity likely results from the diversity of HLA Class II alleles and CD4 T helper cell epitopes stimulating B cell antibody production. Our findings have important implications both for design of new recombinant subunit vaccines as well as for methods of assaying the human antibody response utilizing recombinant proteins produced *in vitro*. [28]

Ovsyannikova et al.:

> Antibody formation in response to antigen stimulation remains the basis for measuring an individual's response and protection for most viral vaccines. A significant proportion of the variation in individual humoral immune response to vaccination appears to be genetic. The collection of genes found on chromosome 6 forming the human leukocyte antigen system provides one of the greatest sources of genetic variation in individuals with respect to their immunological responses. Recent research has demonstrated significant associations between vaccine response and human leukocyte antigen alleles. These associations not only explain why vaccine-induced humoral immune responses vary among individuals and between populations, but these variations may also hold the key to the development of future generations of vaccines. [10]

Men and women differ in the way viral diseases develop (the pathogenesis of the disease). [29-31] A greater inflammatory and cellular immune response is seen in women. Response to vaccination also varies (see table 1 and references therein from [32]).

Poland et al. state:

> The issue of racial and ethnic differences in vaccine response is important, but inadequately studied. For example, early on it was demonstrated that American Indian and Alaskan native populations had decreased humoral immune responses to *Haemophilus influenzae* type b and pneumococcal vaccines [33-35]. Similarly, native Amazon basin tribes demonstrated greater reactivity to measles vaccine [36]. These early studies provide hints of what could be genetically-mediated variations in vaccine responses that if better clarified could inform vaccinology practice. Such advances could require variations in dose and schedule if not substrate of vaccine. Further understanding of the genetic variation in vaccine response may drive an individualization of vaccination for groups and individuals at high risk for vaccine failure or vaccine adverse effects. [17]

Klein et al. evaluated gene response between men and women to the yellow fever vaccine. They analyzed microarray data and found that 660 genes in women, but only 67 genes in men, were differentially expressed after vaccination. They also "established that most of the reported TLR [Toll-like receptor]-associated genes that activate the interferon pathway are upregulated to a greater extent in women than in men during the first 10 days after vaccination." [32] This has implications for both efficacy and adverse reactions.

Table 1.

	Sex difference	Age of study population	References
Rate of vaccination			
TIV, LAIV	F>M	>18 years	7
	M>F	>18 years	8
	F=M	All ages	9
MMR	F=M	6–59 months	10
Rate of seroconversion			
HAV, HBV	F=M	>18 years	11
	F=M	>65 years	12
Humoral immune response			
TIV	F>M	>18 years	13–15
	F>M	>65 years	16–18
17DV	F>M	>18 years	19
BERNA-YF, RKI-YF, ARILVAX, YF-VAX	M>F	>18 years	20,21
AP-YF, 17DD	F=M	>18 years	21,22
RA27/3	M>F	10–17 years	23
Schwarz	F>M	>18 years	24
MMR	F=M	5–10 years	25
	F=M	10–17 years	26
	F>M	10–17 years	27,28
HPV4	M>F	5–17 years	29
HAV	F>M	>18 years	11,30–33
HBV	F>M	6 months to 17 years	34,35
HBV	F>M	>18 years	36–39
HAV, HBV	F>M	>18 years	40,41
HSV-2 gD	F>M	>18 years	42,43
HDCV, PCECV	F>M	>18 years	44,45
Dryvax	F>M	>18 years	46
Attenuated Dengue virus	F>M	>18 years	47
Attenuated Venezuelan equine encephalitis virus	M>F	>18 years	48
Cell-mediated immunity			
MMR	F=M	10–17 years	26,28
RA27/3	M>F	10–17 years	23
HSV-2 gD	F>M	>18 years	49
Adverse reaction			
TIV	F>M	>18 years	14,50,51
		>65 years	16,52,53
17D	F>M	>18 years	54
MMR	F>M	6–59 months	55
	M>F	6–59 months	56
	F>M	5–10 years	57
Attenuated Japanese encephalitis virus	F>M	>18 years	58
Mortality			
Edmonston-Zagreb	F>M	6–59 months	59

TIV and LAIV are vaccines for influenza. MMR is a vaccine for measles, mumps, and rubella. HAV is a vaccine for hepatitis A. HBV is a vaccine for hepatitis B. 17DV, BERNA-YF, RKI-YF, ARILVAX, YF-VAX, AP-YF, 17DD, and 17D are vaccines for yellow fever. RA27/3 is a vaccine for rubella. Schwarz is a vaccine for measles. HPV4 is a vaccine for human papillomavirus types 6, 11, 16, and 18. HSV-2 gD is a vaccine for herpes virus type 2. HDCV and PCECV are vaccines for rabies. Dryvax is a vaccine for smallpox. Edmonston-Zagreb is a vaccine for measles.

Table 1: **Sex differences in response to both childhood and adult virus vaccines**

Humoral immune response to immunization against *H. influenza* also varies with sex with women producing a more robust response. [37-40] Sex differences with other vaccines have been reported (see [32]) Klein et al.:

> Generally, females have greater humoral and cell-mediated immune responses to antigenic stimulation, vaccination, and infection than do males . . . Both basal titres of immunoglobulin and antibody responses to viruses and vaccines are consistently higher in women than in men. Clinical studies reveal that men have lower CD3 and CD4 cell counts, CD4 to CD8 ratios, and Th1 responses. [32]

The above is similar to the differences between men and women seen in response to other drugs and diseases [41-49] and between ethnicities [50-57].

Variation has also been shown in length of immunity. Humans studied during measles outbreaks have revealed that 20-40% of those who manifest the disease had been previously vaccinated. [58] One recent measles outbreak resulted in 155 deaths from approximately 55,000 people infected. There were more than 11,000 hospitalizations and the cost of the outbreak from medical care alone was over $150 million dollars. [59]

The rubella vaccine varies in efficacy and side effects. [6] While 92% to 98% of recipients demonstrate an immune response that is thought to be adequate this translates into a real-life efficacy of 86–97%. Jacobson et al:

> Of Canadian children originally vaccinated at 12 months of age, 92% demonstrated seropositivity by enzyme immunoassay when reimmunised at age 14 years. Seventy-four per cent had evidence of cell-mediated immunity as demonstrated by lymphocyte proliferation. Other studies indicate lower rates of cell-mediated immunity . . .
>
> As implied, there is a measurable primary and secondary failure rate. In one outbreak, 9.8% of all those vaccinated who had been 5 years before developed reinfection. In a resurgence of congenital rubella syndrome in California in 1990, 43% of cases of congenital rubella syndrome occurred among mothers with a history of rubella vaccination. In addition, reinfection clearly risks contagions. Those with subprotective levels of antibodies can become reinfected, this reinfection resulting in viraemia and subclinical infection. The shedding spreads the disease as well as the risk for congenital rubella syndrome. Finally, the vaccine causes both arthralgias and arthritis in 10–40% of susceptible females. Of note, some develop persistent joint reactions [60, 61]. [62]

Jacobson et al have also conducted twin studies and demonstrated a heritable component to rubella vaccine response. [63] Twin studies have also revealed variation in response to other vaccines. [[64] [17, 65]. The Poland papers are also good references for an overview of the subject.]

Multiple genes have been linked to variations in vaccine response (see table 2 from [18]). Single nucleotide polymorphisms, for example, have been reported to influence response. [18] Thomas and Moridani 2010:

> *Similar to interindividual differences in drug response*, a number of currently available vaccines have shown significant differences in the magnitude of immune responses in individuals undergoing vaccination . . . Due to the increasing amount of reports regarding the nonresponsiveness or variations of responsiveness in vaccinated individuals it becomes imperative that researchers have tools such as genomics and proteomics at their disposal to predict which set of population is more likely to develop toxicity to a certain type of vaccine administered. *Furthermore, the norm that, "one size fits all" which was the basis of designing vaccines so far increasingly needs to be reassessed for majority of the vaccines*. [18] (Emphasis added.)

Table 2.

Table 1
Examples of genotype/gene polymorphism related to interindividual variation to vaccination.

Examples of genotypes/gene polymorphisms Vaccine/disease	Responders or a better responders, susceptibility to virus	Non-responders or less responders, resistance to virus	References
Hepatitis	*HLA-DRB1*(*DRB1*0101*, *DRB1*08032*) *HLA-DPA1* (*DPA1*0103*), *HLA-DPB1*(*DPB1*0402*)	*HLA-B46* and *HLA-B15* *HLA-DRB1*(*DRB1*0405*), *HLA-DRB1*07*	Davenport et al. (1995) Hatae et al. (1992) Mineta et al. (1996) Wang et al. (2004)
Measles	*HLA-B*07*	*HLA-B*44*, *HLA-B*8*, *HLA-B*13* *HLA-DRB1*303* *HLA-DPA1*0201*	Jacobson et al. (2003) Jacobson and Poland (2004) Poland et al. (2001)
Mumps	*HLA-DRB1*(*DRB1*303*, *DRB1*01*) *HLA-DQB1*(*DQB1*02*, *DQB1*05*) *HLA-DPB1*(*DPB1*04*) *DQA1*(*DQA1*0101*, *DQA1*0105*)	*HLA-DRB1*(*DRB1*0301*, *DRB1*0801*, *DRB1*1201*, *DRB1*1302*) *DQB1*(*DQB1*0201*, *DQB1*0401*) *DQA1*(*DQA1*0401*, *DQA1*0501*)	Ovsyannikova et al. (2008)
Rubella	*HLA-B*2705*, *HLA-B*4501* *HLA-C*0303*, *HLA-C*0704* HLA class II (*DPB1*0301*, *DQB1*0501*, *DRB1*0101*, and *DRB1*1104*)	HLA class II (*DPB1*0401*, *DPB1*1001*, *DPB1*1101*, *DQB1*0202*, and *DRB1*0701*)	Ovsyannikova et al. (2005a) Ovsyannikova et al. (2004)
Influenza	*HLA-Bw35*	*HLA-DRB1*07* *HLA-DRB1*0701* *HLA-DQB1*0303* and *HLA-DQB1*0603-9/14* HLA-Bw16	Lambkin et al. (2004) Gelder et al. (2002) Cunningham-Rundles et al. (1979) Mackenzie et al. (1977) Spencer et al. (1976)
AIDS		*HLA-DRB1*01*	MacDonald et al. (2000)

Adverse reactions to vaccination are more difficult to study, as the Vaccine Adverse Event Reporting System (VAERS) is a database that consists of self-reports. But there are some data. Stanley et al studied the development of fever after receiving the smallpox vaccine. They examined 19 genes and found that specific haplotypes in the interleukin 18 gene and the interleukin-1 gene complex were associated with an increase in the risk of developing fever. They also found that a haplotype in the interleukin 4 gene was associated with a decrease in the risk of developing fever. [66]

Febrile seizures seem to be associated with the MMR vaccine. [67] Hviid has suggested this as another area that could be studied for genetic variation. [68] (Parents whose children suffered from seizures after a vaccine would consider that a *dramatic difference*.)

Genetic variation influencing vaccine response has also been seen in animals. [69] Leach et al studied response to a peptide challenge in cattle and revealed a clear genetic component. They concluded:

> This study has revealed that both the humoral and cell mediated immune response to a relatively simple 40-mer peptide are under the control of a considerable number of chromosomal loci. [70]

Revaccination also shows intraspecies variability. Some veterinarians require rabies boosters every few years. Jean Greek DVM has her titer measured regularly and has not required a booster for 25 years.

Animal vaccines include parvovirus and distemper for dogs and feline leukemia. David Ramey DVM wrote in his Science-Based Medicine-blog titled Animal vaccinations:

> Yet, in spite of the success of animal vaccination, genuine questions remain as to ideal intervals for booster vaccination. That is, although the effectiveness of vaccination can be shown by reduction in disease, as well as the occasional challenge study (where vaccinated animals are exposed to disease-causing organisms to see if they are protected), no one really knows the "optimum" interval for giving boosters of most animal vaccines.

Clearly, variation exists. This has led to the concept of personalized medicine for vaccines called *vaccinomics*. [71] Poland et al:

> Thus, just as we now recognize that a variety of drugs, such as antidepressant and antihypertensive medications, may require different dosing based on individual genetic differences and result in different side-effect profiles, resulting in variations in therapeutic effect based on genetically-based individual variations; we have now begun to recognize similar attributes in terms of vaccine indications, dosing, side effects and outcomes. As one clinician noted, '…vaccines licensed in the USA are safe and effective. However, not every vaccine is equally safe or equally effective in every person' [[72]]. [65]

Poland et al. 2008:

> However, a "one size fits all" approach could lead to vaccine delivery policies that may ignore future immunogenetics findings. For example, data suggest that up to 40% of the adolescent population develop protective levels of immunity (although the duration of that immunity is unclear) after one to two doses of

> hepatitis B vaccine (HBV) raising the question of whether everyone needs three doses of HBV. In considering issues of vaccine non-responsiveness, a good illustration is HBV, where multiple doses (6 or more) are necessary in some individuals to induce an immune response that in the majority of individuals requires only two or three doses [4]. We might similarly ask the question can we predict who will develop serious side effects after a vaccine, such as neurological complications after vaccinia or yellow fever vaccine. All of these questions expose the need for considering the application of new data emanating from genetics, immunology, molecular biology, bioinformatics, and other fields toward a more personalized or individual approach to vaccine practice [73]. [17]

Poland and colleagues performed extensive research that has associated immune response to vaccines to gene polymorphisms. [17, 74-82]

Because of differences in genes, like SNPs, not all children may be protected by the same vaccine [83, 84] but in the future such children may be able to receive a personalized shot. It is estimated that "between 5 and 20 per cent of people vaccinated against hepatitis B, and between 2 and 10 per cent of those vaccinated against measles, will not be protected if they ever encounter these viruses." [84]

Poland et al 2008:

> Nonetheless, based on work such as what we have discussed above we envision a new "vaccinomics" era of personalized "predictive vaccinology" in the future [74, 85] whereby we might:
>
> - Abandon a one-size (and dose) –fits-all vaccine approach for all vaccines and all persons
> - Predict the likelihood of a significant adverse event to a vaccine [66]
> - Decide the number of doses likely to be needed to induce a sufficient response to a vaccine
> - Design and develop new vaccines and studies to prove their efficacy and safety in such a way as to begin to use them in an individualized manner [86]
> - Identify approaches to vaccination for individuals and groups (based on age, gender, race, other) based on genetic predilections to vaccine response and reactivity

In part, this variation is the result of the fact that, not surprisingly, the immune response is an example of a complex system comprised of networks. Poland et al. 2008:

> Our laboratory has been working on the "immune response network theory" [74]. The basic underlying concept of this theory states that the response to a vaccine is the cumulative result of interactions driven by a host of genes and their interactions and is, therefore, theoretically predictable. The basic genetic elements of the network include genes which activate or suppress immune responses, the dominance profile of a given gene or polymorphism, epigenetic modifications of

> genes, the influence of signaling genes and innate response genes, gene-gene interactions, and genes for other host response factors. While we increasingly understand the role of genetic causes of heterogeneity and treatment effects with drugs this awareness is new in regards to our thinking with the immune response to vaccines . . .
>
> Genetic influences can occur via polymorphisms of a variety of genes involved directly or indirectly in the generation of the immune response. This can include membrane-based viral receptors, innate toll-like receptors (TLRs), signaling molecules, cytokine genes, cytokine receptor genes, human leukocyte antigen (HLA) genes, immunoglobulin Gm and Km allotypes, vitamin A and D receptor genes as well as many others. In addition, it is important to consider the mechanisms for such polymorphism driven effects. These can include differential viral or antigen binding and processing, differential expression/presentation of antigenic peptides, a differential range of presented peptides (genetic restriction), altered secretion patterns, for example of cytokines, altered transcription of important genes such as signaling molecules and gene products, altered binding of virus or antigens by membrane-based receptors, and differential receptor function, expression, and affinities as well as others. [17]

So why have vaccines been so effective? First of all, most of them work in a majority of the population; maybe not 100% of the population but a large percentage nevertheless. But there are other reasons. Infectious disease specialist Mark Crislip wrote the following on Science-Based Medicine, in a blog titled Herd Immunity about why we were able to eradicate smallpox:

> 1) There is only one form of smallpox. Unlike influenza that changes from year to year. So only one vaccine needed.
> 2) By what appears to be a once in a universe miracle, every country cooperated with the WHO (much like we all cooperate with the IRS) so the entire planet received the vaccine. Once enough people were vaccinated, the disease was unable to perpetuate itself and spread and so died out.
> 3) Unlike bacteria, there are no asymptomatic smallpox carrier states. Eradicable viruses usually cause symptomatic disease and do not result in asymptomatic, infectious carrier states that serve as a reservoir for infecting others. HIV and Herpes cause chronic asymptomatic infections and will probably never be eradicated.
> There are other diseases that are theoretically eradicable, like measles and polio. They have one antigenic type, have no carrier state and, if the entire world could be vaccinated, the disease would cease to exist in the wild.

So, one reason some vaccines have been so successful is that the disease in question was vulnerable to intervention and control. Not all infectious diseases are, HIV/AIDS being but one example. Crislip continues:

> The meningococcal vaccine is not one of the stellar vaccines. It has modest efficacy, but may make the difference between life and death in some patients. The meningococcal vaccine can decrease the chance of an individual having invasive disease or dying from the disease, but perhaps more importantly, the vaccine can markedly decrease the asymptomatic carriage rates in a population [87].
>
> The decrease in the number of disease carriers is vital to the prevention of bacterial infections. Vaccines are never 100% effective. Some people are genetically unable to respond to the vaccine, some have immunodeficiencies that preclude receiving vaccines or developing a response to the vaccine, some haven't gotten around to vaccination or are too young to receive a vaccine. If you vaccinate a large number of people, besides preventing disease in an individual, it helps protect the vulnerable in a population.

The meningococcal vaccine is a clear success story fore the above reasons. Even though it not 100% effective it plays a role in preventing death through both herd immunity and directly through its effect on the individual. Crislip continues:

> The vaccine [for pertussis] is good, but not perfect. Vaccine efficacy is 64% for cases defined by mild cough, 81% for paroxysmal cough, and 95% for severe clinical illness [[88] can be accessed at http://jama.ama-assn.org/cgi/content/abstract/267/20/2745]. Note the vaccine is good for attenuating the disease, not preventing it entirely . . . And immunity wanes with time, so older populations are at increased risk for having asymptomatic disease [89].

So again, we see a vaccine that is good but not 100%. Herd immunity and revaccination are important for preventing some infectious diseases. Peter Lipson, an internist writing on Science-Based Medicine, wrote in his blog titled Success in the fight against childhood diarrhea:

> The US has seen a decline in rotavirus disease in the last few years, an effect that appears to be due to increased vaccination and a herd immunity effect.

Crislip continues:

> Part of herd immunity functions to decrease the number of people in a population who carry the disease so that an at risk population are not exposed. Part of herd immunity functions by preventing the spread of some, especially viral, diseases. If there are not enough vulnerable people in a population, the disease cannot spread and perpetuate.

Vaccinations can be an important and effective tool in the infectious disease arsenal by simply decreasing the number of people capable of spreading the disease even when they are not effective in 100% of individuals. A combination of efficacy, herd immunity,

changes to the environment in the form of decreasing the numbers of the vector and so forth has resulted in the very dramatic reduction, or elimination, of certain infectious diseases. This is very impressive! But society, especially scientists, should not leap to the conclusion that this reduction must mean that vaccines are almost 100% effective in almost 100% of individuals.

In conclusion, variation exists among humans (and other species) in response to vaccines. Some of these differences are less important than others, however dramatic differences exist both in terms of efficacy and side effects.

Relevance of this discussion for claims regarding animal models

Animals and humans have much in common. The laws of science apply to animals and human alike. Throw a dog or human from an airplane and each will hit the ground at approximately the same time. Gravity affects each the same. The canary in the coalmine can act as a warning to all carbon-based lifeforms that require a certain partial pressure of oxygen. Microbes can infect humans and animals alike; but it is on this level that things start to get interesting. As the system under study becomes more complex, or the system is evaluated at a higher level of organization, it is going to be more difficult to predict whole-organism level responses based on reductionism, vis-à-vis HIV kills humans not chimpanzees. The concept of vaccination, because it works in more or less the same way—on the same pathways and response—in the same species, can be applied to more or less all members of that species. The intraspecies differences in response can be explained by differences in genes, age, and so on. These genetic differences are even more profound between species. It is when we try to extrapolate between species that the differences between complex systems manifest in an even more dramatic fashion.

As we have seen, vaccines are effective in a majority of people and a majority of the time. There are variations (some dramatic) in efficacy, duration, and side effects but all in all the practice/concept has been shown effective. The variations in response have been and are being linked to genetic differences and vaccinomics is in the future. If a vaccine is effective in you today, then there is a very high probability that it will be effective in me. Not 100%, but with the numbers we saw above, it is high enough that scientists would consider vaccination a viable practice or intervention.

One mistake naïve nonscientists and even professional scientists (usually nonphysicians) make when discussing vaccines is that they think that vaccines are *all or none*. They either work or they don't. As we have seen, a more sophisticated understanding is required. The same is true of animal models. Vivisection activists try to sell society on the notion that animal models either work or they don't and since they obviously have given us *some* knowledge in the past, the practice *per se* must be effective. This is an example not only of the false dichotomy fallacy but also the fallacy of equivocation since the phrase *animal model* or *animal research* is used to mean more than one concept. The use of animals as *predictive models* is justified by appealing to the use of animals as *heuristic devices* and so forth. Different uses but the same name. This is very disingenuous on the part of the vivisection activist. As we have stated many times, animals can be successfully used in some areas of science and research, but not to predict

human response to drugs and disease. [1-3] That is why we routinely distinguish among the various uses and vivisection activists do not.

This leads us to a major reason why vaccination is considered a success and animal models when used to predict human response to drugs and disease are not. Probability. Vaccines are considered a success because of the relative uniformity of response—intraspecies predictive ability is high. Conversely, animal models when used to predict human response to drugs and disease are failures because of the interspecies variation. We have covered elsewhere the reasons why animal models fail to predict drug and disease response for humans as well as the empirical evidence supporting this claim. [1, 2] Therefore, I will here merely very briefly summarize and give a few examples.

From *Animal Models in Light of Evolution* (p358):

> Our position can be summarized as follows: Living complex systems belonging to different species, largely as a result of the operation of evolutionary mechanisms over long periods of time, manifest different responses to the same stimuli due to: (1) differences with respect to genes present; (2) differences with respect to mutations in the same gene (where one species has an ortholog of a gene found in another); (3) differences with respect to proteins and protein activity; (4) differences with respect to gene regulation; (5) differences in gene expression; (6) differences in protein-protein interactions; (7) differences in genetic networks; (8) differences with respect to organismal organization (humans and rats may be intact systems, but may be differently intact); (9) differences in environmental exposures; and last but not least; (10) differences with respect to evolutionary histories. These are some of the important reasons why members of one species often respond differently to drugs and toxins, and experience different diseases. Immense empirical evidence supports this position.

The above could be considered the theory that allows us to place the empirical evidence in context.

Examples of empirical evidence would include the following.

A study of 23 chemicals revealed only 4 were metabolized the same in humans and rats. [90] One does not need to calculate positive and negative predictive values in order to ascertain that this data is consistent with the position that animal models do not predict human response. 4 out of 23 is not good.

Johnson et al. 2001 found that out of 39 anticancer drugs tested on xenograft mice, only 1 mimicked the response in humans. [91] One does not need to calculate positive and negative predictive values in order to ascertain that this data is consistent with the position that animal models do not predict human response. 1 out of 39 is not good.

Ennever et al:

> . . . of the 20 probable human non-carcinogens with conclusive animal bioassay results, only one, methotrexate, is negative, and the other 19 are positive . . . Thus, the standard interpretation of animal bioassay results provides essentially no differentiation between definite human carcinogens and probable human non-carcinogens. [92]

A study [93] examined six drugs, the side effects of which were already known in humans. The study found that animals correctly identified 22 side effects, but incorrectly identified 48 side effects that did not occur in humans, while missing 20 side effects that did occur in humans. This yields the following:
Sensitivity (Sn) = 22/(22+20) =52%
Positive Predictive Value (PPV) = 22/(22+48) = 31%

Lumley, in 1990 showed that animals did *not* identify 67% of toxicities that occurred in humans. [94] Even without knowing Sn and PPV, failing 67% of the time is not good.

Litchfield [95] studied rats, dogs, and humans in order to evaluate responses to 6 drugs. Only side effects that could be studied in animals were calculated. The data is below.

Man	Toxic effects found in man	53
	Toxic effects found in man only	23
Rat	Toxic effects also found in man	18
	Toxic effects not found in man	19
Dog	Toxic effects also found in man	29
	Toxic effects not found in man	24

Rat

19 false positives
35 false negatives
Sn = 18/(18+35) = 34%
PPV = 18/(18+19) = 49%

Dog

24 false positives
24 false negatives
Sn = 29/(29+24) = 55%
PPV = 29/(29+24) = 55%.

Patrick McGee, Senior Editor of *Drug Discovery & Development* April 2006:

> In the early 1990s, when employed at Merck & Co., Rakesh Dixit, PhD, started working on a neurokinin-1 (NK1) receptor antagonist for depression. NK1, a peptide, had been implicated in the depression process and Merck created a "huge" program to block NK1 with a new mechanism of action that differed from

> the selective serotonin reuptake inhibitors then on the market, says Dixit, who is now senior director of toxicology, drug evaluation at Johnson & Johnson Pharmaceutical Research and Development (J&JPRD), La Jolla, Calif.
>
> "In the animal models, the drug worked beautifully. We had all the evidence of efficacy, the drug was hitting the receptor, but we went into humans and the drug failed miserably.
>
> . . . We found out the wrong way that neurokinin-1 did not play that important a role in the depression process as the animal models or publications were telling us. That's an expensive way to find out something is not working. If we had a better animal model of depression, we would have gotten a better answer."

Jonas et al. in *Ann N Y Acad Sci* 2001: “Agents claimed to be neuroprotective in animal stroke models have *all* failed in human trials.” [96] (Emphasis added.) One does not need to calculate positive and negative predictive values in order to ascertain that this data is consistent with the position that animal models do not predict human response. When the numerator is zero, you really know all you need to know about the predictive ability of the model. The denominator, in this case the number of drugs that were neuroprotective in some animal model, has to be approaching 100 by now. Regardless, *zero* makes a powerful statement.

The number of HIV vaccines that have shown effectiveness in monkeys also now approaches 100. None have been effective in humans. Once again, one does not need to calculate positive and negative predictive values in order to ascertain that this data is consistent with the position that animal models do not predict human response. Further, the nonhuman primate models misled researchers about the mechanisms by which HIV gains entrance to the cell, among other things. [97] [98] [99] [100] [101]

Other notable failures include:

The fact that scientists thought, secondary to animal studies, that smoking did not cause cancer. [102] [103] [[104] p133] Coulston and Shubick:

> For decades the clinical observation of an association between cigarette smoking and bronchial carcinoma was subject to unfounded doubt, suspicion, and outright opposition, largely because the disease had no counterpart in mice. There seemed no end of statisticians craving for more documentation, all resulting in the fateful delay of needed legislative initiative [105].

The belief that asbestos was safe. Smith et al.:

> In contrast to statistical association between exposure to asbestos and development of cancer in man, a large literature on experimental studies has failed to furnish any definite evidence for induction of malignant tumors in

> animals exposed to various varieties and preparations of asbestos by inhalation or intratracheal injection. [106]

And the notion that high cholesterol was good for your health. [107, 108] [[109] p510]

For more references and example, see our books and articles. The above are not anecdotes and they are from fields as disparate as heart disease, stroke research, HIV research, and toxicology. Animal models cannot predict human response to drugs and disease. This is a fact not just about toxicity testing but about diseases and drugs in general. Some apparently do not understand this point. In response to my blog about chimpanzees and vaccines, LifeScientist wrote:

> We are familiar with your arguments about predictivity, and while those those [sic] arguments may have some merit when applied to toxicology (though I think you are still very unrealistic in your expectations there), they miss the point entirely when it comes to basic and applied biomedical research.

The evidence in our books and articles, like that presented above, refute this point. We have stated repeatedly that basic research, which is research that is not designed to be predictive [110], is viable and is not subject to the same *type* of scrutiny as research that claims to be predictive. Applied animal-based research makes the claim to be predictive and fails, when analyzed, to fulfill the claim. (Using sentient animals in basic research is subject to a different type of scrutiny; see Is the use of sentient animals in basic research justifiable? [110] for more.)

We are not *unrealistic* in our criticism of animal models in applied research in general or toxicity research in particular. We are assessing claims made by those in the field. We did not set up a straw man of prediction; those in the field make the claim that their models are in fact predictive. (See *Animal Models in Light of Evolution* for more, including examples of the researchers making the claim of prediction in writing.)

The above debacles (e.g., smoking and asbestos are safe) are not small indiscretions either. People died because data from animal models led to predictions that were simply wrong. The empirical evidence, from all fields, supports our position that animal models cannot predict human response to drugs and disease. The knowledge gained from the fields of complex systems and evolutionary biology provides the framework, or theory, that allows us to place the empirical evidence in a greater context.

Vaccines have been tested for centuries and found effective. They work! We can say this because of the data. We also have a *theory*, in the form of current knowledge of basic human physiological principles, that not only allows for the empirical evidence but also predicts it. We can also explain the empirical evidence that dramatic differences exist even with a modality as successful as vaccination. Small differences in genetic makeup can lead to one person being immune to a disease after vaccination while another is not. The same is true of side effects.

Why answer such questions?

Before I address this issue, I need to comment on some of the complicating factors that influence and or explain the various arguments offered against Shanks' and my position.

As I have often stated, if the reader wants a thorough understanding of our position, she needs to read *Animal Models in Light of Evolution*. Students need at least a year to even partially appreciate Organic Chemistry or other complicated science subjects. Similarly, the position we present requires study and cannot be explained in sound bites. So it is disingenuous for the vivisection activist to argue with sound bites or to ask us to explain our position with sound bites. You cannot answer all the questions in the textbook on Organic Chemistry after listening to a one-hour lecture or reading a blog or attending a debate. But just as Duane Gish the creationist proponent does in his lectures, you can ask very misleading and nonsensical questions that your opponent's argument appear silly. When vivisection activists use the same tactics, the scientific and skeptical communities should call them out.

Shanks and I have said many times that animal models cannot predict human response to drugs and disease. This position requires:
1. An understanding of the philosophy of science vis-à-vis what the word *predict* means in biological science and what role theory plays in science;
2. An understanding of complex systems and evolutionary biology;
3. An appreciation of the empirical evidence; and perhaps most importantly
4. An honest approach to the question. If you have a vested interest in using animals and think that our position will negatively impact your ability to do just that, you might not be entirely honest in your questions or tactics. I will present the arguments and comments of the vivisection activists and let the reader decide for himself whether honest intent exists.

As I said earlier, all of the controversial aspects of essay (except the part about there being variation to vaccines, which should have been known already by any competent scientist) could have been derived from our book *Animal Models in Light of Evolution*. Niall Shanks, Jean Greek, and I have covered this ground many times in lectures, articles [2, 3], debates, and even blogs. If anyone wanted a serious discussion, he would first make sure he was familiar with out position then criticize it based on science and the rules of critical thinking. Instead, we see responses like those with which that I started this essay ("Is AFMA anti-vaccination!?" An example of association fallacy as well as others) and the below.

LifeScientist wrote:

> .....where scientists don't yet know everything about human biology, and despite the great ongoing efforts of basic science around the world are unlikely to for some decades yet, we all realise that it is impossible to predict with 100% accuracy the outcome of any treatment in an individual person from previous studies, whether those are in vitro, in animal models or even in other people.

This is a straw man, as we do not claim that anything has to be right 100% of the time in order to be predictive. That is why science makes use of statistics like positive and negative predictive values. Outside the laws of science, one rarely sees anything that is 100% predictive. For medical science, a PPV and NPV in the 0.9 neighborhood seems reasonable. The figures for acceptability in medical science can vary with circumstances but nobody accepts a PPV of 0.6 as predictive for human response to drugs and disease.

LifeScientist continues:

> So what!

Well, actually LifeScientist, it *is* a big deal when an animal model wrongly forecasts that a drug will be safe and the manufacturer goes to clinical trials on that basis and the drug kills people. It is also a big deal when animal models say asbestos is safe so it continues to be used or when animal do not contract cancer from smoking and so forth. People die from these mistakes. It would be one thing if those using animal models made no claims for prediction but they do and therefore they must answer for being wrong. The animal model has now been studied sufficiently and we know enough about other areas of science (consilience) to say that animal models cannot predict human response to drugs and disease.

LifeScientist continues:

> With the various models available to us we can learn and predict enough to proceed from discoveries made in basic research through the development and refinement of candidate treatments, vectors etc in applied research and on to translation to human trials.

Nice rhetoric but I have seen no data to support this position. If LifeScientist wanted to claim that we can learn things in basic research that might someday help people then fine. But that is not what he said and indeed that is not what many scientists say when applying for grants or when justifying their use of animals to society. They say animal models predict human response. "As soon as we learn how to cure cancer in mice, we can cure it in humans." (See *Animal Models in Light of Evolution* for similar quotes.) But this demonstrably false because, as Dr. Richard Klausner, then-director of the National Cancer Institute stated:

> The history of cancer research has been a history of curing cancer in the mouse...We have cured mice of cancer for decades—and it simply didn't work in humans. [111]

In a lab, if you are trying to correlate variables, a correlation of 0.6 might be a good number. But in the real world things are different. In the real world, if 25% of people do not respond to a vaccine or other drug, that is a big deal. Likewise if 5% of people taking a drug or vaccine die or are permanently injured that is also a big deal. Drugs get recalled for less dramatic side effects.

LifeScientist, from another post about the same blog:

> Greek's council of despair
> So what would Ray Greek have scientists do, just take a punt and jump straight to immunizing chimps and gorillas in the wild in what would be effectively a large phase II or phase III clinical trial?

This another straw man. I did not take a stand on what would be the appropriate way to test vaccines for wild animals, I was merely pointing out that there were ethical issues as well as scientific ones. Even if the science worked, there would be an ethical debate about whether we should test vaccines, intended for wild chimpanzees, on captive chimpanzees. I certainly did not imply that we should "punt and jump straight to immunizing chimps and gorillas in the wild." This is false dichotomy: test on captive animals or wild ones will die. There are other options. For instance, we could test on wild animals by darting them with the vaccine the darting them again at a later date and measuring titers, Frankly, I have no idea how to administer or test vaccines on wild animals. That is not my area of expertise. But by criticizing what I did *not* say or imply LifeScientist is avoiding the issue I *am* addressing. Also, by making it appear that I would like to "punt and jump straight to immunizing chimps and gorillas in the wild," he makes me appear uncaring about the animals. That is the fallacy of appeal to emotion as well as, in this case, an *ad hominem*.

LifeScientist continues:

> Or do we give up on the idea of vaccination altogether until our knowledge of the chimpanzee and gorilla immune systems is so complete that we can predict the effectivness [sic] of of [sic] a vaccine without ever testing it in vivo before hand?

Another straw man and *ad hominem*. He is making it appear that I want to abandon helping chimpanzees and gorillas. He is also accusing me of making the *perfect solution* fallacy—since the solution is not perfect, it is no good at all. I did not say or imply that we should give up on the idea of vaccination until a perfect solution was reached.

LifeScientist continues:

> Should scientists have waited until personalized medicine became a reality before attempting to develope [sic] vaccines? We'd still be waiting for many very effective vaccines that have saved millions of lives and prevented much disability if we'd done that, vaccines whose development relied in almost all cases on both animal and clinical research.

More of the same.

Neon-armadillo writing in response to another one of my blogs:

> It is hardly news that different species have genetic differences.
> In drug discovery research, the effect of such differences can be minimized by choosing an animal model with the best match for whatever disease is being investigated. If better models are available it is absurd to suggest that research would not use those better models. But humans are not always the way to go in the early stages of drug discovery research. Perhaps Dr. Greek approves of using sick children as research subjects, but many parents would understandably rather have a few mice sacrificed in the search for new drugs to help alleviate the suffering of their children. Dr. Greek's heartless approach to drug research may be good for the lab mice, but it will be pure misery for the people who require medical attention for illnesses that are currently untreatable.

There are several problems here. 1. Drug companies admit that their animal models are not predictive (see the Dixit quote above for an example, also see our books, articles and my blogs), so if neon-armadillo wants to claim such animal models exist he should produce data. 2. The *ad hominem* that I prefer to use sick children speaks for itself. 3. We are not arguing that mice should be saved instead of humans; we are arguing that mice do not predict human response to drugs and disease

Examples like this indicate that the people criticizing our position are not serious about science. They are vivisection *activists* that want to see vivisection continue for nonscientific reasons. That is actually fine, as we have freedom of speech and people can advocate for whatever they want. But as my mother used to say: "Just because a jackass brays, does not mean you have to answer." Answering nonsensical arguments and fallacies is not going to convince the portrayers of those arguments of *anything*. They are not arguing *science*, they are arguing in an attempt to mislead the reader. This should inform the scientific community *and* raise red flags concerning why scientists would forsake science and become activists for something that is refuted by science.

So why answer the questions and criticisms of the vivisection activist when they consist largely of fallacies such as *ad populum* arguments, *ad miscordium*, straw man, the fallacy of equivocation, *ad hominems*, association fallacy, and so forth?

There is now way to silence someone who does not want to understand a position. But, by making the fallacious arguments, the vivisection activists give me the opportunity to once again point out to the unbiased reader the fact that the vivisection activists cannot refute our scientific arguments and thus must fight with misleading sound bites, faulty science, and nonsense. While I cannot answer ever single nonsensical argument, *ad hominem* attack, misrepresentation of science, or other fallacy (there are not enough seconds left in the universe) I do try to address the ones I think society in general might have an interest in. Having done that with the vaccine question, the vivisection activist will now ask the same question in a different way. In hopes that by so doing he can once again to mislead the reader, uneducated in this area, into believing the vivisection activist has something intelligent to say. Or the vivisection activist will pick on some inconsequential point of this essay and take great issue with it. Or, he will ask another nonsensical question and, when I ignore it, will claim victory for his side. What the

vivisection activist will not do is engage in a scientific discussion regarding the use of animals as predictive models either in the form of a debate or a point-counterpoint in the scientific literature. That should cause concern for even the most ardent fan of animal models and vivisection activists.

Conclusion

The bloggers at the Science-Based Medicine website, among others, make much of *prior probability*. Before deciding whether to waste resources, for example my time in responding to nonsense or money for animal models that claim to be predictive or money to test treatments like homeopathy, it is helpful to calculate what the probability is that spending the resources will result in a viable outcome. In other words, that you will accomplish your goal, whatever that goal may be. Since there is absolutely no scientific basis for thinking that homeopathy will work and much good science for thinking it will not, the unbiased person would not choose to spend money testing homeopathy.

This is not without precedence. The US Patent Office does not test claims for perpetual motion machines as such a machine would be in direct violation of a law of science (hence it is impossible). Watchdog groups frequently use prior probability when criticizing how the government spends money. For example, in mandating impossible guidelines for an industry or enterprise, funding projects with a track record of failing, seeking to explain nonsense, and so forth. As another example, society does not fund projects in medial research looking for mechanisms for the four humours hypothesis of disease. The evidence and theory supporting the four humours of disease (phlegm, yellow bile, black bile, and blood) is nonexistent hence the enterprise is not funded.

Society needs to ask about prior probability when deciding whether to fund animal models that claim to be able to predict human response to drugs and disease.

I will close with the following from Massimo Pigliucci:

> Perhaps the most appropriate question for us in this chapter, which can be applied to all the pseudoscience we have briefly examined, is the one that *Nature* reporter Lucy Odling-Smee asked in the piece on the closing of the PEAR lab: "how permissive should science be of research that doesn't fit a standard theoretical framework, if the methods used are scientific?" In other words, how many times do we have to show that alleged instances of telepathy, clairvoyance, telekinesis, ufos, ghosts, psychic abilities, astrological forces, and the rest of the shebang can better be explained by perfectly normal means? There is, of course, no simple answer to this question, as the appropriate amount of resources and time to devote to the investigation of fringe science depends on how important the claims would be if they turned out to be true, how many times they have been disproved before, and, frankly, how limited the resources of scientists and universities are in practice. We hear repeated calls from ufologists, parapsychologists, psychics, and astrologers to keep an open mind, and there are certainly examples of skeptics who close the door to further investigation a bit too quickly, as in the case of the Campeche UFOs recounted above. But, as astronomer Carl Sagan once aptly put

it, you do not want to keep your mind so open that your brain is likely to fall out. [112] p82-3

Acknowledgements

I could have essentially written vaccine portion of this essay using only material from the bloggers at Science-Based Medicine. I in fact did use much material that I found there and thank the bloggers for sharing their expertise. I also want to acknowledge that many of them do not share our views on animal models.

I apologize for all the [sic] notes that accompany the blog quotes. I blog and if anyone quotes me they will have lots of [sic] notes. There should be a rule about ignoring typos in blogs.

I also want to thank the journals *The Lancet Infectious Disease* and *Toxicology* for use of the tables.

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