The imperative to vaccinate

The disease legacy of civilization

We are almost certainly the most diseased species on earth. If you have small children, you probably don't need convincing, but to put some figures behind this assertion, by one accounting there are nearly 1400 human pathogens, including bacteria, fungi, prions, protozoa, viruses and worms, and of these, 100-150 appear capable causing human epidemics[1,2]. We human beings are remarkable in many ways, but why are we remarkable for playing host to so many infectious agents? Why is it that we must maintain high levels of vaccine coverage to prevent infectious agents from sickening or even killing large swaths of the population? The answers lie in the story of human disease epidemics, and it begins with human cultural and technological ascendance and what we now understand to be its inevitable consequences for pestilence and death. It is about our ingenuity, which has caused the retreat of many infectious diseases, but highlights a central tension in human existence—immediate self-interest vs. long-term collective welfare[3]. The concept is not just academic; there are real world implications that we can resolve with an understanding of human disease ecology. The notion is that we are not only culturally connected or genetically connected through a common ancestry. Rather, there is another fundamental concept that is, perhaps, not widely accepted or even understood. We are biologically connected, in the present, through our exchange of infectious agents and our common susceptibility to disease.

To understand modern human disease prevalence, we have only to look to the most basic principles of epidemiology. A simplified version is that diffuse or small host populations cannot sustain an acutely infectious agent, meaning one in which infection is followed by clearance and long-term immunity. As the host population density decreases, the number of transmission events that can occur during the infectious stage of the disease also decreases until the infectious agent is not maintained within the population. This would apply to our pre-agricultural ancestors—a few thousand individuals spread out over an enormous area. But, the population was not evenly distributed. Our ancestors almost certainly congregated at high density but in small groups. In such a host population, an acutely infectious disease might quickly spread through the group, but then run out of new susceptible hosts[4].

The idea is that small or low-density populations can only sustain a certain type of infectious agent, one that persists, usually for the life of the host[5 6]. Once infected with cytomegalovirus or Epstein-Barr virus (herpes viruses), which most of us are, we are infected for life, and such viruses have infected us since even before we became human beings. To some extent, this was the primordial state of disease in diffuse bands of pre-agricultural hunter-gathers: persistent viruses, bacteria (e. g., tuberculosis), intestinal protozoa, worms, fleas, etc. Our Paleolithic

ancestors were not disease-free, but they almost certainly did not experience periodic and devastating epidemics[7,8].

Conversely, large populations that live at high density, such as modern human beings, can sustain a much greater diversity of infectious agents including those that the immune system is able to clear. Transmission from person to person is rapid enough and continuous, such that there is little selective pressure for persistence. Large urban populations can maintain acutely infectious agents indefinitely due to a constant source of newly susceptible hosts in the form of immigration or births. These agents often share an ability to be transmitted by casual contact such as respiratory droplets produced by a cough or a sneeze. There are over 200 different viruses from at least six different virus families (adenovirus, coronaviruses, influenza virus, parainfluenza virus, respiratory syncytial virus and rhinovirus) that cause "cold" symptoms: sneezing, coughing, and runny nose[9]—and there is good reason for all this discomfort. These are the efficient means for transmitting respiratory viruses that circulate and thrive in large, high-density populations. We can (and do) prove this concept when we send our children to day-care centers or pre-schools. How many colds do they bring home in their first two years of school, and how easily are these colds spread to parents and friends?

The dawn of agriculture and the domestication of animals, especially herd animals, allowed the emergence of permanent human settlements and the growth of situated populations[10]. The world's population increased about 1000-fold from the beginning of the agricultural revolution to the end of the 19th century, and most importantly, settlements eventually begat huge massing of humanity. Simultaneously, we domesticated animals and ourselves, and we sampled all of the viruses and bacteria existing in cows, horses, pigs, sheep, goats and birds. Those that could replicate in human beings and spread from person to person by respiratory propulsion (or other means, such as sewage) became established evermore in the human population. This is the answer to why we are the most diseased species on earth. We are the only species to so profoundly and rapidly change the way in which we interact with each other and other animals, in other words, we invented for ourselves an entirely new ecosystem. So in addition to the endless parade of cold viruses that circulate among us, we acquired infectious agents that cause diphtheria, influenza, measles, meningitis, mumps, plague, rubella, smallpox, typhus, whooping cough, and many other diseases. Each disease has its own history and severity, but all rely on large high-density populations for continued propagation.

These newly acquired infectious agents not only caused severe or deadly disease, they shaped the population. Many are known as childhood diseases because they infect susceptible children who either recover from the disease and retain immunity, or die. In a population in which a disease like measles existed, everyone contracted the virus exactly once such that almost all surviving adults were immune. What does the world look like in the face of measles? From 1956

to 1960, before the availability of a vaccine, an average of 542,000 cases of measles were reported each year in the U.S. with an average of 450 measles-related deaths, 4000 encephalitis cases (often with permanent brain damage), and 150,000 respiratory complications. The measles vaccine was licensed in 1963 and the measles, mumps, rubella (MMR) vaccine was licensed in 1971. For the years between 1987-2000 the number dropped to 28,730 cases of measles in children under 5 yrs; 97 died, 43 contracted encephalitis, and 2480 contracted pneumonia. Since 1997 there has been less than 1 case per million population in the US[11]. The global burden of measles in 1999 was an estimated 873,000 deaths that were reduced through a world-wide vaccination campaign to an estimated 164,000 deaths in 2008[12].

Those who survive measles without lasting effects still have two worries. One is that measles infection depresses the immune system for up to two years making children more susceptible to other infections[13], and a second is the possibility of developing subacute sclerosing panencephalitis (SSPE), a usually fatal neurologic degenerative disease caused by reactivation of latent measlesvirus. The risk is about 4-11 per 100,000 measles cases, but is much higher among children who contract the disease before the age of 2. SSPE can occur at any time for the rest of the patient's life with an average of 7 years following the acute disease. For children who are immunocompromised, such as those being treated for leukemia, an actual measles infection is severe, extended, and often fatal.

While measles is possibly the world's most infectious human virus, it was not the most devastating of the childhood infectious diseases—that accolade goes to smallpox. The smallpox death toll for just the 20th century has been estimated at upwards of 300 million people, similar to the entire population of present day United States[14]. Smallpox caused more deaths than all the wars in history. For centuries before widespread vaccination, most urban families could count on losing multiple children to diseases such as smallpox, diphtheria, scarlet fever, or whooping cough. With widespread vaccination, we have greatly reduced or, in some cases, essentially eliminated the disease. The death toll for smallpox in the 21st century, nil—it has been eliminated as an infectious disease on earth.

Connected by infectious disease

Smallpox eradication was our first and thus far only complete victory over a human disease-causing agent, made possible by strong compliance to universal vaccination. After tortuous millennia of epidemic disease and hundreds of millions dead, who would argue that this was not a most wonderful gift given by mankind to itself? But that gift was not without cost, and the cost was a tincture of personal independence and the acknowledgement that each of us is inextricably tied to the entire human community. It took the idea of community out of the realm of philosophy and placed it as a fundamental property of life. Smallpox eradication itself was a physical enactment of the tension between personal freedom and the authority of society. In, "On Liberty" in Chapter IV, John Stuart Mill asks, "What then is the rightful limit to the sovereignty of the

individual over himself? Where does the authority of society begin? How much of human life should be assigned to individuality, and how much to society?"

Mill's inquiries can be answered by biology, but first consider the concept of herd immunity. As the density of susceptible (unvaccinated or disease naïve) hosts declines so does the incidence of disease. An important point is that, below a certain threshold, the incidence of disease (frequency of new infections), even in unimmunized people, approaches zero. This is herd immunity, and it follows directly from basic epidemology. It effectively reduces the size and density of the disease-susceptible population making acutely infectious agents unsustainable[15]. Conversely, since vaccine protection is sometimes imperfect, a vaccinated individual living within a disease susceptible population is at substantial risk. *The risk of disease for any individual is thus most importantly dependent on the collective immunity of the population*, especially those most susceptible to infection, usually the youngest children and oldest adults.

In this regard, disease ecology does not equivocate; in the world as it exists today, our health and our very being depend on the immune status of the rest of humanity. The rightful limit to the sovereignty of the individual over himself stops at the boundary of disease immunity. As long as one case of smallpox could be found on earth, billions were at risk. Even without considering the imperative of contagious disease, Mill came to the same conclusion, "As soon as any part of a person's conduct affects prejudicially the interests of others, society has jurisdiction over it…" Two centuries before "On Liberty" and before the Enlightenment, this was expressed after a fashion in John Donne's Meditation XVII, "Now this bell tolling softly for another, says to me, Thou must die" written while he was convalescing from a near fatal disease, possibly typhus. While this meditation was ostensibly concerned with God as the author of every person and every death, we might equally apply it in a way that Donne could not—we are each of a network, a medium for disease that transcends us as individuals. We can rage against this injustice, but it is literally a fact of life. In this context, I can't help but quote the famous line from Meditation, "No man is an island, entire of itself."

Who does not vaccinate and why?

Herd immunity is a fundamental concept with no strict definition. The threshold is sharp but not definite. It requires compliance, but not strict compliance. It protects those unable to comply as effectively as those unwilling. It is the most powerful force in disease prevention but exists only in the immunity status of the entire population network. Considering the difficulty of this concept, it is no wonder that as a society and as a people we do not have a unified consensus concerning the responsibility of individuals to vaccinate their children.

One way to understand vaccination decisions is as an exercise in game theory played out over the entire human population of the earth. In this case, each individual is defined narrowly in economic terms, acting as if he or she balances

costs against benefits to maximize personal advantage. If most everyone cooperates (vaccinates) then everyone enjoys the benefits of being disease free. On the other hand, the decision to cooperate may be perceived to have a cost, and individuals looking to maximize personal advantage will choose non-cooperation at a certain probability. When no one is vaccinated and everyone is in danger, that probability is close to zero. This must have been the dominant sentiment in the time of smallpox. As universal vaccination is approached, danger diminishes, and the probability of non-cooperation increases. In other words, as we proceed toward elimination of a disease, as we are for poliomyelitis, the invisible hand of the market pulls defeat from the jaws of victory. From this reasoning, elimination of disease on a purely voluntary basis has been proposed to be unlikely, and the thought is that compliance to protect the population or eradicate a disease can only be achieved by a mandatory vaccination policy[16].

In the Western Hemisphere we have all but eliminated measles, mumps, and rubella, in once sense, moving us backward in time to the pre-Columbian rarity of acutely infectious diseases. But, should we lapse in our vaccination vigilance, within one generation we could replay the disease devastation of the 16th century that included death of more than half of the native inhabitants of the Western Hemisphere. We are part of, what Watts and Strogatz called, a small-world network[17]—with no more than six-degrees of separation connecting the entire 7 billion human beings on earth. Like the spread of the newly identified MERS from the Middle East to Korea, we can consummate those connections, wherever they may be, with a day's travel. A glimpse of a future with poor vaccine compliance occurred last year with an outbreak of measles originating at the "happiest place on earth," in Anaheim, California. The infecting individual (patient zero) almost certainly arrived from abroad, but most of the infected individuals were unvaccinated U. S. residents[18].

In addition to community health, the notion of not vaccinating seems to deny short-term self-interest. Even with a low disease incidence brought about by herd immunity, do you really want to take the risk of your child contracting whooping cough? Beyond that, universal vaccination protects children with immunodeficiencies, either congenital or those that arise from cancer treatment. It can eliminate a disease from the world for all time saving all future generations. And what is the cost? There are many articles published in peer-reviewed journals that have described the adverse reaction rate associated with the recommended schedule for pediatric vaccines. I cannot do justice to them here, but one number stands out. A million. For almost all vaccines the rate of adverse reactions per vaccine dose appears to be on the order of one in one million[19]. I say appears because the events are so infrequent, they are difficult to distinguish from the rate of adverse events in untreated children. At a much higher rate, one in 2000, U.S. children have a primary immunodeficiency, and such children should not be inoculated with a live vaccine such as the MMR vaccine.

For everyone else, vaccination is at least 99.9999% safe. In particular, the completely discredited Wakefield publication purported to show a connection between autism and MMR[20,21]. Since then, study after study, and meta-studies (a study of studies) indicate that there is "strong evidence that MMR vaccine is not associated with autism"[19]. This means that MMR vaccination does not result in a significantly increased rate of autism in the whole population, but the studies did not consider the question of whether children who may be genetically predisposed to autism are affected by vaccination. In a recent study, this issue was addressed. From a database of almost 100,000 children, the incidence of autism spectrum disorder (ASD) was compared between children who had an older sibling with or without ASD. The study found that receipt of MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD[22]. We do not have a credible biological basis for theorizing that provoking an immune response through immunization causes mental disorders, and with more than a decade's analysis of millions of children, no connection has been found.

Aside from sober risk assessment, sticking an infant with a sharp needle to induce symptoms of fever and soreness might feel, unnatural. But it isn't so. The immune system is naturally engaged on a continuous basis, and there is an entire body of work to support this. Perhaps a most telling but horrible example comes from the AIDS epidemic. Before the availability of anti-retroviral drugs, the human immunodeficiency virus (HIV) would cripple and then kill off but one component of the immune system (a type of T lymphocyte) and the previously friendly flora and fauna of the body would become deadly: cytomegalovirus found in the majority of adults would cause severe diseases such as retinitis; candida commonly found on the skin, mouth or reproductive tract would cause thrush; an ever-present fungus, previously known as *Pneumocystis carinii* (now *Pneumocystis jirovecii*), would cause pneumonia; normally benign toxoplasma could cause severe or fatal toxoplasmosis, and many other environmental agents became deadly as T lymphocytes disappeared[23]. Regardless of the presence of actual disease-causing agents, without the constant activity of our immune system, we perish. Additionally, natural, as the world has developed in the last few thousand years, that is without vaccines, is the agony of a child dying from whooping cough, or paralysis caused by poliomyelitis, or mental retardation caused by measles. Naturally, families lose children due to infectious disease.

I recognize that medical studies are difficult to sort out. The wisdom of one moment is often replaced in the next. A reasonable course of action with respect to new clinical findings is to wait and act conservatively. However, we now have a century's worth of experience in vaccinating billions of people. We have witnessed the regression or elimination of many infectious diseases in the face of vaccination. And we have studied the short and long-term effects of vaccination. This is now established science. We can work to make vaccines even more

effective, but we cannot as a society regress to some past era where we count hundreds of thousands of measles or polio cases per year.

Infectious diseases are a major, and almost certainly permanent part of human existence. The growth of civilization with addition of animal domestication made the appearance of epidemic diseases inevitable, but because our inventiveness knows no bounds, we have found countermeasures that relieve at least some of our collective misery. Furthermore, the experience of humankind over the past several millennia has shown that we have no choice; our place in the network of hosts susceptible to human pathogens gives lie to our notions of complete personal independence. Even the most atavistic society would not choose for their children a path of immune naiveté (at least not for long). Perhaps this is an instructive irony. It takes deadly infectious diseases to see that we are all of a one species, biologically connected, and isolated on earth.

I believe most people are capable of sorting out scientific investigation from the writings and postings of cynical alarmists. I would like to suggest that for this important decision, parents refrain from everyone's favorite pastime, bias confirmation. For any given topic we can readily find someone on-line who confirms our preconceived notions. This is not research, and it is not the way to make life or death decisions. The academic medical community is almost never in perfect accord, and we love to prove each other wrong. But in this case, I would venture we are of one mind.

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