The Imperative to Vaccinate

Stephen M. Hedrick, PhD

The Disease Legacy of Civilization

Human beings are almost certainly the most diseased species on earth. By one accounting, there are at least 1400 human pathogens, including bacteria, fungi, prions, protozoa, viruses, and worms, and of these, 100-150 appear capable of causing human epidemics.[1,2] Even this is likely to be an underestimate, as new and sensitive sequencing techniques continue to uncover new viruses at a steady rate.[3] 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.[4] 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 number of people with immunity increases, the density of susceptible hosts decreases, and with the corresponding decline in transmission, the infectious agent is not maintained in the population.[5] This principle described our preagricultural ancestors—a few thousand individuals congregated in groups but spread out over an enormous area.

Small or low-density populations can only sustain a certain type of infectious agent, one that persists, usually for the life of the host.[6,7] Once infected with herpes viruses, such as herpes simplex virus, cytomegalovirus, or Epstein–Barr virus, we are infected for life, and such viruses have infected us since even before we became human beings.[8-11] To some extent, this was the primordial state of disease in diffuse bands of preagricultural hunter–gathers: persistent viruses, bacteria (eg, *Mycobacterium tuberculosis*), intestinal protozoa, worms, and fleas. Our Paleolithic ancestors were not disease-free, but they almost certainly did not experience periodic and devastating epidemics.[12,13]

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 and dense 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, and as evidence of the success of this pathogen strategy, there are more than 200 different viruses from at least 6 different virus families (adenovirus, coronaviruses, influenza virus, parainfluenza virus, respiratory syncytial virus, and rhinovirus) that cause "cold" symptoms: sneezing, coughing, and runny nose.[14]

The dawn of agriculture and the domestication of animals, especially herd animals, allowed the emergence of permanent human settlements and the growth of large situated communities.[15] The world's population increased approximately 1000-fold from the beginning of the agricultural revolution to the end of the 19th century, and most importantly, settlements eventually grew into a 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 fecal–oral) 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 a great many deadly infectious agents, such as those that cause diphtheria, influenza, measles, meningitis, mumps, plague, rubella, smallpox, typhus, whooping cough, and others. Each disease has its own history and severity, but all rely on large, high-density populations for continued propagation.

MMR	Measles, mumps, rubella
VICP	Vaccine Injury Compensation Program

From UC San Diego, Molecular Biology, La Jolla, CA

Supported by R01AI037988 and R01AI131081. The author declares no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.06.041

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 US, along 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 and 2000, the number dropped to 28 730 cases of measles in children younger than 5 years of age; 97 died, 43 contracted encephalitis, and 2480 contracted pneumonia. Since 1997, there has been less than 1 case per million population in the US.[16] 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.[17]

Those who survive measles without lasting effects still have 2 worries. One is that measles infection depresses the immune system for up to 2 years, making children more susceptible to other infections,[18] and a second is the possibility of developing subacute sclerosing panencephalitis, a usually fatal neurologic degenerative disease caused by reactivation of latent measles virus. The assessed risk is on the order of 1 in 10 000 measles cases and as much as 10-fold greater for children who contract measles before the age of 12 months.[19] For children who are immunocompromised, such as those being treated for leukemia, an actual measles infection is severe, extended, and often fatal.[20]

Although measles is possibly the world's most infectious human virus, it was not the most devastating of the childhood infectious diseases. The smallpox death toll for just the 20th century has been estimated at upwards of 300 million people, similar to the entire population of the present-day US.[21] Smallpox caused more deaths than all the wars in history. For centuries before vaccination, most urban families could count on losing multiple children to smallpox, diphtheria, scarlet fever, or whooping cough. With widespread vaccination, combined with targeted vaccination to insulate the last few cases, smallpox was 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 universal, global vaccination, and intensive surveillance. After tortuous millennia of epidemic disease and hundreds of millions dead, who would argue that this was not a most wonderful gift given by humankind 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 community protection (often referred to as "herd immunity"). As the density of susceptible (unvaccinated or disease naïve) hosts declines, so does the incidence of disease. Below a certain threshold, the incidence of disease (frequency of new infections), even in unimmunized people, approaches zero. This is community protection, and it follows directly from basic epidemiology. Vaccination effectively reduces the number and density of the disease-susceptible people, making acutely infectious agents unsustainable in the population.[22] Conversely, because 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 him or herself 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. Although 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. The death of one of us portends many more. We can rage against this injustice, but it is literally a fact of life. In this context, the famous line from Meditation is relevant, "No man is an island, entire of itself."

Who Does Not Vaccinate and Why?

Community protection is a fundamental concept with no strict definition. The threshold is sharp but varies with each infectious agent. It protects vaccinated and unvaccinated people alike. 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 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. In contrast, the decision to cooperate may be perceived to have a cost, and individuals looking to maximize personal advantage will choose noncooperation at a certain probability. When no one is vaccinated and everyone is in danger, that probability is close to zero—everyone is incentivized to vaccinate or risk the possibility of deadly disease. This must have been the dominant sentiment in the time of smallpox. As universal vaccination is approached, danger diminishes with or without vaccination, and the probability of noncooperation increases. For measles, the threshold for community protection is calculated to be 94.4%, that is, when 94.4% of the population has received 2 doses of MMR vaccine, the community is protected from disease.[23] Under such conditions, some parents may decide not to vaccinate and thus avoid even very rare adverse effects. The consequence of this is that the rate of vaccination drops below the threshold, and the community is no longer protected. In other words, as we proceed toward elimination of a disease by vaccination, as we are for poliomyelitis, the invisible hand of the market pulls defeat from the jaws of victory. From this reasoning, elimination of a 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.[24]

In the Western Hemisphere, we have all but eliminated measles and rubella, in one sense moving us backward in time to the pre-Columbian rarity of acutely infectious diseases. However, 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 one-half of the native inhabitants of the Western Hemisphere.[25] We are part of, what Watts and Strogatz called, a small-world network[26]—with no more than 6 degrees of separation connecting the entire 7+ billion human beings on earth. Like the spread of Middle East respiratory syndrome 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 adherence occurred not too long ago, with an outbreak of measles originating in Anaheim, California. The infecting person (patient zero) almost certainly arrived from abroad, but most of the infected individuals were unvaccinated US residents.[27]

The decline in MMR vaccination compliance began with a 1998 medical report in the journal *Lancet*. Andrew Wakefield and 12 colleagues published an analysis of 12 children claiming to show a connection between MMR vaccination and the onset of a newly described "pervasive developmental disorder" that they summarized as a "chronic enterocolitis in children that may be related to neuropsychiatric disorder." At face value, this is a tiny sample size with no controls. It linked 3 common conditions with MMR vaccination based on parent's recollections. Multiple large studies subsequently showed no such association, and the paper was retracted by 10 of the authors and by the journal after a prolonged study by the General Medical Council in the United Kingdom; however, it was not just a case of flawed science, it turned out to be fraud driven by avarice. In articles published by the *British Medical Journal*, the investigative journalist Brian Deer revealed how Wakefield had been hired to attack the MMR vaccine by a lawyer, Richard Barr. Wakefield and colleagues were paid to contrive the existence of a syndrome, he initially called, "autistic enterocolitis" for the express purpose of bringing a class action lawsuit against vaccine manufacturers; this occurred before initiation of the disgraced study.[28] Another apparent moneymaking scheme was ironically to market vaccines. In a press conference given after the publication of his *Lancet* paper, Wakefield said he could not support the triple MMR vaccination and called for vaccination to each disease separately. He had previously patented a single measles vaccine. The British General Medical Council revoked his license to practice medicine, and he was asked to leave the Royal Free Hospital in London.

The Wakefield study has no basis in reality, but its publication corresponded to a substantial drop in MMR coverage in the United Kingdom, Europe, and the US.[29] In response, some countries or states within the US have made vaccination a mandatory condition for entrance into schools. For example, California Senate Bill No. 277, signed into law June 2015, requires vaccination for all children attending any public or private elementary or secondary school, childcare center, day nursery, nursery school, family daycare home, or development center. Exemptions for described medical conditions are permitted, but those based on personal or religious beliefs were to be phased out. Because California requires vaccination records for all schools, the effects of the bill could be tracked—and the effects were dramatic. In 2014, more than 33% of school children lived in California counties with vaccination rates less than 90%, and 70% of children lived in counties with less than a 95% vaccination rate.[30] Interestingly, the counties with the lowest rates of vaccination were of 2 types, rural counties largely located in the most northern part of the state and counties that include the tony urban communities surrounding San Francisco and Los Angeles.[31] By 2016, more than 95% of children were from counties with greater than 95% vaccination. Nonetheless, the law only requires vaccination records for students as they enter each grade span (kindergarten, seventh grade, etc), and it recognizes personal exemptions previously on file. As such, there are still schools in which a single case of measles could spark a local epidemic.

Contrast the vaccination rate in California, where comprehensive vaccination is required to attend school, with that of Oregon, where exclusions based on personal beliefs are allowed with only a requirement for completing an informational module online.[32] The proportion of the population in Oregon counties with kindergarten vaccination rates greater than 95% has gone from almost 100% in 2000 to just 30% as of 2015.[30]

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 community protection, pertussis vaccination is a small price to pay for the prevention of whooping cough. Beyond that, universal vaccination protects children with immunodeficiencies that arise either from congenital or acquired conditions and their treatments. It can eliminate a disease from the world for all time, saving all future generations, but at what cost? What is the safety of vaccination?

The Safety of Vaccination

Each vaccine from each manufacturer is reviewed by the Food and Drug Administration for safety before licensing, and after licensing, the Centers for Disease Control and Prevention and Food and Drug Administration maintain a nationwide monitoring system, the Vaccine Adverse Event Reporting System, a signal detection system to identify rare events not found in prelicensing reviews. The program allows anyone to report an adverse reaction online, by FAX, or by mail.[33] The Centers for Disease Control and Prevention also operates the Vaccine Safety Datalink in conjunction with US care organizations that track data from more than 9 million people. These data provide the means to monitor the safety of current and recently introduced vaccines nearly in real-time as they are administered to people across the country. The data from the Vaccine Safety Datalink are used to devise the vaccine regime for children and assess the frequency of complications as they arise.[34]

There also exists a national Vaccine Injury Compensation Program (VICP), run by the Health Resources and Services Administration. This program receives reports of adverse vaccine reactions, studies each claim, and makes 1 of 3 determinations: (1) an adverse reaction occurred "more likely than not"; (2) the individual is compensated, although the panel does not concede that there occurred a vaccine-related adverse reaction; and (3) the case is adjudicated by a court within the US Court of Federal Claims. Because the VICP is the only avenue for vaccine-related compensation in this country, the number of filed cases is one measure of the number of adverse reactions severe enough to incite a claim.

For the years of 2006 through 2013, there were approximately 2.2 billion vaccine doses distributed in the US. The total number of cases brought before the VICP was 2853, and the number ultimately compensated was 1672. That is, about 1 in a million vaccine doses was associated with some sort of adverse reaction severe enough to bring a patient to the VICP. Importantly, this is but an average for all vaccines and all groups of people, but it highlights the overall rarity of vaccine-associated, severe adverse events. Considering the benefit to the individual and to society, this would seem to be a reasonable risk.

Aside from sober risk assessment, sticking an infant with a needle to induce an immune reaction might feel unnatural. But it isn't so. The immune system is naturally engaged and constantly fighting many potential infections on a continuous basis. For example, in people with an acquired immunodeficiency, such as those low numbers of T lymphocytes, previously benign bacteria, fungi, and viruses become deadly: cytomegalovirus, candida, *Pneumocystis carinii* (now *Pneumocystis jirovecii*), toxoplasma, and other environmental agents can cause sickness or death.[35] Regardless of the presence of actual disease-causing agents, without the constant activity of our immune system, we perish. Another concern is that multiple vaccinations might "overload" the immune system, causing children to be more susceptible to unvaccinated diseases. However, in a study of nonvaccine-targeted infections recorded from emergency department visits, there was no significant correlation with the number of vaccines given to children 24-47 months of age.[36]

Medical studies are difficult to evaluate, even for professionals. 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 safer and more effective, but we cannot as a society regress to some past era in which 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 the addition of animal domestication made the appearance of epidemic diseases inevitable, but human inventiveness has allowed us to find 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. ■

Submitted for publication Jan 26, 2018; last revision received Jun 1, 2018; accepted Jun 13, 2018

Reprint requests: Stephen M. Hedrick, PhD, UC San Diego, Molecular Biology, 9500 Gilman Dr, La Jolla, CA 92093-0377. E-mail: shedrick@ucsd.edu; smorrisonhedrick@gmail.com

References

1. Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. Philos Trans R Soc Lond B Biol Sci 2001;356:983-9.
2. Woolhouse M, Gaunt E. Ecological origins of novel human pathogens. Crit Rev Microbiol 2007;33:231-42.
3. Rosenberg R, Johansson MA, Powers AM, Miller BR. Search strategy has influenced the discovery rate of human viruses. Proc Natl Acad Sci USA 2013;110:13961-4.
4. Wilson EO. The meaning of human existence. New York: Liveright; 2014.
5. May RM. Network structure and the biology of populations. Trends Ecol Evol (Amst) 2006;21:394-9.
6. Black FL. Measles endemicity in insular populations: critical community size and its evolutionary implication. J Theor Biol 1966;11:207-11.
7. Galvani AP. Epidemiology meets evolutionary ecology. Trends Ecol Evol (Amst) 2003;18:132-9.

8. McGeoch DJ, Cook S, Dolan A, Jamieson FE, Telford EA. Molecular phylogeny and evolutionary timescale for the family of mammalian herpesviruses. J Mol Biol 1995;247:443-58.
9. Cohen JI. Epstein-Barr virus infection. N Engl J Med 2000;343:481-92.
10. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 2010;20:202-13.
11. Wertheim JO, Smith MD, Smith DM, Scheffler K, Kosakovsky Pond SL. Evolutionary origins of human herpes simplex viruses 1 and 2. Mol Biol Evol 2014;31:2356-64.
12. Black FL. Infectious diseases in primitive societies. Science 1975;187:515-8.
13. Harper KN, Armelagos GJ. Genomics, the origins of agriculture, and our changing microbe-scape: time to revisit some old tales and tell some new ones. Am J Phys Anthropol 2013;152(suppl 57):135-52.
14. Heikkinen T, Jarvinen A. The common cold. Lancet 2003;361:51-9.
15. McNeill WH. Plagues and peoples. New York: Anchor Books/Doubleday; 1976.
16. Roush SW, Murphy TV. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007;298:2155-63.
17. Moss WJ, Griffin DE. Measles. Lancet 2012;379:153-64.
18. Mina MJ, Metcalf CJ, de Swart RL, Osterhaus AD, Grenfell BT. Vaccines. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science 2015;348:694-9.
19. Wendorf KA, Winter K, Zipprich J, Schechter R, Hacker JK, Preas C, et al. Subacute sclerosing panencephalitis: the devastating measles complication that might be more common than previously estimated. Clin Infect Dis 2017;65:226-32.
20. Naniche D. Human immunology of measles virus infection. Curr Top Microbiol Immunol 2009;330:151-71.
21. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization; 1988.
22. Anderson RM, May RM. Vaccination and herd immunity to infectious diseases. Nature 1985;318:323-9.
23. Plans-Rubio P. Why does measles persist in Europe. Eur J Clin Microbiol Infect Dis 2017;36:1899-906.
24. Bauch CT, Earn DJ. Vaccination and the theory of games. Proc Natl Acad Sci USA 2004;101:13391-4.
25. Mann CC. 1491: new revelations of the Americas before Columbus. New York: Alfred A. Knopf Incorporated; 2005.
26. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature 1998;393:440-2.
27. McCarthy M. Measles outbreak linked to Disney theme parks reaches five states and Mexico. BMJ 2015;350:h436.
28. Deer B. Wakefield's "autistic enterocolitis" under the microscope. BMJ 2010;340:c1127.
29. Deer B. How the case against the MMR vaccine was fixed. BMJ 2011;342:c5347.
30. Oster E, Kocks G. After a debacle, how California became a role model on measles. New York Times. January 16, 2018. https://www.nytimes.com/2018/01/16/upshot/measles-vaccination-california-students.html. Accessed July 17, 2018.
31. Karlamangla S, Lin II R. Vaccination rate jumps in California after tougher inoculation law. Los Angeles Times. April 13, 2017. http://www.latimes.com/local/lanow/la-me-ln-california-vaccination-20170412-story.html. Accessed July 17, 2018.
32. Oregon Health Authority. Getting Immunized, Oregon Immunization Program. https://www.oregon.gov/oha/ph/PreventionWellness/VaccinesImmunization/GettingImmunized/Pages/non-medical-exemption.aspx. Accessed July 17, 2018.
33. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2015;33:4398-405.
34. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine 2014;32:5390-8.
35. Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis 2002;34:1098-107.
36. Glanz JM, Newcomer SR, Daley MF, DeStefano F, Groom HC, Jackson ML, et al. Association between estimated cumulative vaccine antigen exposure through the first 23 months of life and non-vaccine-targeted infections from 24 through 47 months of age. JAMA 2018;319:906-13.