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# The History Of Vaccines And Immunization: Familiar Patterns, New Challenges

If we could match the enormous scientific strides of the twentieth century with the political and economic investments of the nineteenth, the world's citizens might be much healthier.

by **Alexandra Minna Stern and Howard Markel**

**ABSTRACT:** Human beings have benefited from vaccines for more than two centuries. Yet the pathway to effective vaccines has been neither neat nor direct. This paper explores the history of vaccines and immunization, beginning with Edward Jenner's creation of the world's first vaccine for smallpox in the 1790s. We then demonstrate that many of the issues salient in Jenner's era—such as the need for secure funding mechanisms, streamlined manufacturing and safety concerns, and deep-seated public fears of inoculating agents—have frequently reappeared and have often dominated vaccine policies. We suggest that historical awareness can help inform viable long-term solutions to contemporary problems with vaccine research, production, and supply.

**T**HE GASPING BREATH AND DISTINCTIVE SOUNDS of whooping cough; the iron lungs and braces designed for children paralyzed by polio; and the devastating birth defects caused by rubella: To most Americans, these infectious scourges simultaneously inspire dread and represent obscure maladies of years past. Yet a little more than a century ago, the U.S. infant mortality rate was a staggering 20 percent, and the childhood mortality rate before age five was another disconcerting 20 percent.<sup>1</sup> Not surprisingly, in an epoch before the existence of preventive methods and effective therapies, infectious diseases such as measles, diphtheria, smallpox, and pertussis topped the list of childhood killers. Fortunately, many of these devastating diseases have been contained, especially in industrialized nations, because of the development and widespread distribution of safe, effective, and affordable vaccines.

Indeed, if you asked a public health professional to draw up a top-ten list of the achievements of the past century, he or she would be hard pressed not to rank im-

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munization first.<sup>2</sup> Millions of lives have been saved and microbes stopped in their tracks before they could have a chance to wreak havoc. In short, the vaccine represents the single greatest promise of biomedicine: disease prevention.<sup>3</sup>

Nevertheless, the story is more complicated than it might appear at first glance. Even as existing vaccines continue to exert their immunological power and new vaccines offer similar hopes, reemerging and newly emerging infectious diseases threaten the dramatic progress made. Furthermore, obstacles have long stood in the way of the production of safe and effective vaccines. The historical record shows that the development of vaccines has consistently involved sizable doses of ingenuity, political skill, and irreproachable scientific methods. When one or more of these has been lacking or perceived to be lacking, vaccination has engendered responses ranging from a revised experimental approach in the laboratory to a supply shortage and even insurrection in the streets. In short, vaccines are powerful medical interventions that induce powerful biological, social, and cultural reactions.

### **Edward Jenner, Cowpox, And Smallpox Vaccination**

We begin our history of vaccines and immunization with the story of Edward Jenner, a country doctor living in Berkeley (Gloucestershire), England, who in 1796 performed the world's first vaccination.<sup>4</sup> Taking pus from a cowpox lesion on a milkmaid's hand, Jenner inoculated an eight-year-old boy, James Phipps. Six weeks later Jenner variolated two sites on Phipps's arm with smallpox, yet the boy was unaffected by this as well as subsequent exposures.<sup>5</sup> Based on twelve such experiments and sixteen additional case histories he had collected since the 1770s, Jenner published at his own expense a volume that swiftly became a classic text in the annals of medicine: *Inquiry into the Causes and Effects of the Variolae Vaccinae*. His assertion "that the cow-pox protects the human constitution from the infection of smallpox" laid the foundation for modern vaccinology.<sup>6</sup>

How did Jenner, a country doctor, formulate the vaccine concept? To begin with, his discovery relied extensively on knowledge of the local customs of farming communities and the awareness that milkmaids infected with cowpox, visible as pustules on the hand or forearm, were immune to subsequent outbreaks of smallpox that periodically swept through the area. Moreover, a learned man immersed in the secular and rational doctrines of the Enlightenment, Jenner applied the scientific methods of observation and experimentation to this parochial wisdom, ultimately conducting one of the world's first clinical trials. He thus was able to devise an alternative to variolation (the controlled transfer of pus from one person's active smallpox lesion to another person's arm, usually subcutaneously with a lancet), which had been practiced in Asia since the 1600s and in Europe and colonial America since the early 1700s.<sup>7</sup>

Jenner also profited from his training as a wide-ranging generalist with a broad knowledge of science and medicine. For example, before devoting himself to pri-

vate practice, Jenner focused on natural history, penning well-respected studies of the cuckoo and the dormouse.<sup>8</sup> In fact, Jenner was so skilled a naturalist that he was invited (although he declined) to join Captain Cook's second voyage to the South Seas to classify flora and fauna.

Jenner's interest in natural history and animal biology sharpened his medical understanding of the role of human-animal trans-species boundaries in disease transmission. He experienced the proverbial "Eureka"-like moment sometime during the 1770s, after hearing a Bristol milkmaid boast, "I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face."<sup>9</sup> Two decades later he translated that farming lore into the guiding principle of his cowpox inoculation hypothesis. His cognizance that animals were implicated and necessary for vaccine production was truly prescient; it foreshadowed later use of cows, guinea pigs, rabbits, and even chicken eggs in vaccine production. However, this breach of the species barrier also made many people wary of and sometimes hostile to the idea of consciously introducing foreign animal products into their own bodies. During the early 1800s, for example, there was no shortage of cartoons mocking Jenner and depicting the transmogrification of the recently vaccinated into sickly cows and fantastical beasts.<sup>10</sup>

■ **Beyond cowpox.** Although Jenner's milkmaid experiments may now seem like quaint fables, they provided the scientific basis for vaccinology. This is all the more striking given that our current conceptions of vaccine development and therapy are now much more encompassing and firmly rooted in the science of immunology. Until the brilliant French chemist Louis Pasteur developed what he called a rabies vaccine in 1885, vaccines referred only to cowpox inoculation for smallpox. Although what Pasteur actually produced was a rabies antitoxin that functioned as a post-infection antidote only because of the long incubation period of the rabies germ, he expanded the term beyond its Latin association with cows and cowpox to include all inoculating agents.<sup>11</sup> Thus, we largely have Pasteur to thank for today's definition of *vaccine* as a "suspension of live (usually attenuated) or inactivated microorganisms (e.g., bacteria or viruses) or fractions thereof administered to induce immunity and prevent infectious disease or its sequelae."<sup>12</sup>

■ **Changing terminology, constant challenges.** Even though *vaccination* and *immunization* are often used interchangeably, especially in nonmedical parlance, the latter is a more inclusive term because it implies that the administration of an immunologic agent actually results in the development of adequate immunity.

As the definitions of *vaccine*, *vaccination*, and *immunization* have changed over time, becoming more scientifically precise, many of the basic patterns and problems of vaccinology have remained constant. In particular, issues of funding have been central to the steady development and distribution of vaccines, as have concerns with contamination and safety. Furthermore, public reactions to vaccines are usually quite strong, even as they have varied from awe of a seeming scientific miracle to skepticism and outright hostility. Beyond the far-reaching microbio-

logical and immunological discoveries that have transformed vaccinology over the past century, vaccinology has been shaped increasingly by regulations governing human-subjects research and the enforcement of sterilization and safety standards. Especially after World War II, as exemplified by the exacting standards demanded by Thomas Francis Jr. in the polio field trials of 1954, the ethical design and execution of vaccine research has become a core concern for many stakeholders.<sup>13</sup>

## Funding And Patronage

As acceptance of his discoveries grew, Jenner was praised and feted by the British aristocracy and quickly became a celebrity in the cosmopolitan town of Cheltenham, where he had moved his family in the 1790s.<sup>14</sup> In the first decades of the nineteenth century, the British Parliament awarded Jenner the equivalent of more than a million dollars in today's currency, and Oxford, Cambridge, and Harvard Universities, as well as many scientific societies, bestowed honors on him.<sup>15</sup>

As Jenner became a celebrated figure across Europe, "Jennerian inoculation" became the sine qua non for burgeoning national health programs. Kings and presidents seized upon mass-scale vaccination campaigns in an effort to demonstrate their forward-looking stance toward science and their commitment to the health of their citizenry. By 1800, for instance, 100,000 people had been vaccinated in Europe, and vaccination had begun in the United States, spearheaded by Harvard professor Benjamin Waterhouse and President Thomas Jefferson.<sup>16</sup> From Spain, King Charles IV sent the Balmis Expedition to the Americas in 1803 to introduce smallpox vaccination to its colonies. Before disembarking on the Royal Expedition of the Vaccine, Francisco Xavier de Balmis rounded up five Madrid orphans for the voyage. They served as an arm-to-arm transfer chain to keep the vaccine fresh until they arrived at the Caribbean.<sup>17</sup>

■ **International investment.** Since Jenner's discovery, governments have often invested, albeit unevenly and incompletely, in vaccines. Initially vaccines were considered a matter of national pride and prestige. They quickly became integral to utilitarian and public health notions of societal security, productivity, and protection. In Europe and North America during the nineteenth century, for instance, smallpox vaccination was made compulsory under state laws. In the twentieth century, as the standard battery of childhood immunizations, including diphtheria, measles, mumps, and rubella, was developed, vaccination was frequently managed or adjudicated by governmental entities (from the municipal to the federal) and eventually was required for public school attendance.

After the founding of the World Health Organization (WHO) and related organizations such as the United Nations Children's Fund (UNICEF), vaccine programs went global. In 1974, for example, the WHO launched the Expanded Programme on Immunization (EPI), with the goal of dramatically increasing vaccination rates among children in developing countries. For more than three de-



for vaccine stockpiles at the top of its list of recommendations.<sup>26</sup> Nevertheless, capital infusions have not been immediately forthcoming from either the public or the private sector. Given our current predicament, we could learn a great deal from the enthusiastic financial support granted to Jenner and early smallpox vaccination efforts. Although royal patronage is no longer an option, financial incentives, whether through tax relief or guaranteed purchase, may be needed to ensure an adequate and steady vaccine supply.

### **Manufacture, Distribution, And Safety**

Jenner's initial experiments were carried out in a pre-germ theory era that lacked modern methods of quality control and sterilization. Hence, the prospect of contamination constantly loomed over smallpox vaccine development, and many people were rightly wary of contracting another dread disease via inoculation. With a method that often involved extracting lymph from pustules on the arms of those recently vaccinated, it was not uncommon for existing microorganisms to accompany the vaccine from arm to arm, spreading diseases such as erysipelas, syphilis, and scrofula.<sup>27</sup>

Unlike most drugs, which are essentially chemical agents, vaccines are biologic agents that can be compromised during processing. Whether killed-virus, whole-cell, bacterial, or live-attenuated, vaccines can be disrupted at various points along the journey from the laboratory to the vial. Not surprisingly, quality control, sterilization, and monitoring have become non-negotiable for vaccine production. Even with strict standards, however, the possibility of contamination remains (even though it is far less likely today than several decades ago). In addition, vaccine production must be closely supervised to ensure that vaccines induce immunity and do not produce serious infection. For example, the optimism about the polio vaccine in spring 1955 was temporarily muted after 200 children contracted disease (fatal for five children) from a vaccine containing active wild-type polio virus that was manufactured by Cutter Laboratories in California.<sup>28</sup>

Debates over virulence, killed versus live virus, and antigenic strains have played a critical role in setting the parameters of the production and manufacture of safe and effective vaccines for more than one hundred years. The controversy between Jonas Salk, who advocated a killed polio vaccine, and Albert Sabin, who preferred a live polio vaccine, characterizes this divide, although there are many more examples.<sup>29</sup> For instance, as measles immunization was becoming widely accepted in the United States in the 1960s, a formalin-inactivated vaccine licensed in 1963 was withdrawn because it induced short-lived immunity and predisposed recipients to atypical measles syndrome if they were exposed to the wild-type measles virus. Ultimately safe and reliable vaccines were developed from the original Edmonston B strain (initially isolated by John Enders and Thomas Peebles in human and monkey cell cultures in 1954).<sup>30</sup> One of these at-

tenuated vaccines, the Moraten strain, is the only measles vaccine used in the United States today, while two additional strains—the Schwarz and Edmonston-Zagreb—are employed in worldwide immunization campaigns against a disease that infects approximately thirty million children per year, killing approximately 750,000 of them.<sup>31</sup> In the case of BCG (bacillus Calmette-Guérin) vaccination against tuberculosis, developed in France in 1921, concerns about efficacy and safety led to very different patterns of vaccine acceptance. In Scandinavia, BCG was mass-distributed as part of the emergence of a comprehensive social welfare program. Conversely, in the United States and Britain, acceptance was much slower because of greater confidence in the long-term benefits of tuberculosis testing and treatment and apprehension that mass BCG vaccination might misconstrue the results of mass-scale tuberculin Mantoux PPD (purified protein derivative) testing by delivering large numbers of false positives.<sup>32</sup>

### Protesting Vaccines

Especially in the 1830s, after an initial generation had been vaccinated and the incidence of smallpox had declined markedly in the United States and Europe, a vociferous antivaccination movement emerged.<sup>33</sup> Sometimes antivaccinationists were protesting what they considered the intrusion of their privacy and bodily integrity. Many working-class Britons, for example, viewed compulsory vaccination laws, passed in 1821, as a direct government assault on their communities by the ruling class.<sup>34</sup> In addition, by the mid-eighteenth century the rise of irregular medicine and unabashed quackery encouraged antivaccinationism. For instance, irregulars generally viewed vaccination as a destructive and potentially defiling procedure of heroic medicine, akin to blood-letting.<sup>35</sup> In addition, antivivisectionists, who abhorred animal experimentation, sometimes joined forces with antivaccinationists.<sup>36</sup>

To a great extent, nation-states responded by articulating that they possessed the right to immunize for the “common good.” In 1905, for example, the U.S. Supreme Court ruled in *Jacobson v. Massachusetts* that the need to protect the public health through compulsory smallpox vaccination outweighed the individual’s right to privacy.<sup>37</sup> Barring exceptions for religious belief, which exist in all but two U.S. states, this tenet has been consistently reiterated and is lent scientific muster by the concept of “herd immunity,” whereby a certain target of the population—approximately 85–95 percent, depending on the disease—must be immunized for protection to be conferred upon the entire group.<sup>38</sup>

Until quite recently, historical studies frequently depicted all antivaccinationists as irrational and antiscientific. This characterization was misguided. If we interpret antivaccinationists on their own terms and by applying historical context, we can see that many behaved as rational actors who were weighing the pros and cons of inoculation. While nineteenth-century fears of vaccination might have been based on anecdotal horror stories of other infections, the statis-

tical risks of vaccine-induced infection from that era would not be medically acceptable today.

In addition, many vaccine critics do not reject immunization outright but instead emphasize issues of safety and efficacy or are opposed to specific, but not necessarily all, vaccines. The passage of the 1986 National Childhood Vaccine Injury Act (NCVIA), spearheaded by parents troubled by a putative link between vaccination and neurological problems, illustrates that legislators and scientists alike continue to be exceedingly concerned with the issue of vaccine safety.<sup>39</sup> In the past decade in particular, parents and their watchdog groups have raised important questions about the purported link between a noticeable rise in autism and the preservative thimerosal (previously used in diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, or Hib, and hepatitis B vaccines). Even though a series of scientific studies have demonstrated that there is no causal connection between thimerosal and autism, in 1999 the U.S. Food and Drug Administration (FDA), in conjunction with the U.S. Public Health Service and the American Academy of Pediatrics, ceased to license thimerosal-containing vaccines. Similar claims about a causal link between MMR and autism have also been alleged and sometimes sensationalized by the media. Not surprisingly, the suggestion that vaccinating one's child might lead to developmental disorders has fostered unease among many parents. Clearly, American parents need better access to and clearer explanations of the recent findings published in medical journals that confirm the lack of a link between thimerosal or MMR and autism or other neurological conditions.<sup>40</sup> However, as indicated by recent political and medical debates about the need for Americans, especially first responders, to be vaccinated against smallpox in case of a bioterrorism attack, and the hundreds of Gulf War soldiers who have rejected anthrax vaccinations, antivaccinationism will not fade away any time soon.

## **Elusive Vaccines And The Ethics Of Vaccine Research**

It took more than eighty years after Jenner's discovery for scientists to develop new vaccines. With the bacteriological revolution, which began in the 1880s, came high hopes that the identification of specific disease-causing microbes would lead directly to the development of specific inoculating agents. Although spectacular vaccines have been produced since that time, changing the course of human history, vaccines for many diseases remain elusive.

■ **Malaria.** One of the most frustrating quests has been for a malaria vaccine. The most common parasites responsible for malaria (plasmodia) have demonstrated an impressive ability to circumvent eradication efforts by becoming drug-resistant. The fact that the WHO recently announced that it was exceedingly pleased with a new vaccine that protects just 30 percent of those immunized indicates the immense difficulty of producing a malaria vaccine. Although this percentage is very low compared with other vaccines, given the severity of malaria worldwide and the fact that

it kills more than one million and infects more than 300 million children a year, even such limited coverage could save thousands if not millions of lives in the hardest-hit areas of the globe.<sup>41</sup>

■ **HIV.** No discussion of vaccines is complete without assessing the potential of an HIV vaccine in the twenty-first century. Like plasmodium, the HIV retrovirus is a wily and insidious microbe. Most attempts to develop an HIV vaccine have ended in failure. Recently, the Gates Foundation launched an initiative aimed to develop and eventually distribute effective TB and HIV vaccines.<sup>42</sup> As with other global health endeavors, there are crucial cultural and ethical questions to consider.<sup>43</sup> Because some of the most promising vaccines are being tested on vulnerable and impoverished populations in sub-Saharan Africa, organizations such as the HIV Vaccine Trials Network (HVTN) and the International AIDS Vaccine Initiative (IAVI) emphasize the importance of heeding the ethical guidelines promulgated in documents such as the 1947 Nuremberg Code and 1979 Belmont Report.<sup>44</sup> In this sense, immunization has been deeply affected by changing historical contexts and norms; especially since the 1970s, it has not been possible to launch vaccine trials and campaigns involving human subjects without clear-cut protections against human experimentation and medical abuse.

### **Lessons Learned**

Our struggle with germs is endless and can be neither completely halted nor assuaged by vaccines, no matter how great their immunological power. Sadly, effective vaccines for two of the world's leading killers, HIV and malaria, remain in the research stage. Furthermore, even the most knowledgeable scientist cannot precisely predict the strain of next year's influenza, nor can an expert epidemiologist always explain why certain diseases rise and burn out at particular rates. Molecular biology, genomics, and proteomics will certainly reveal a great deal about similar antigens and foster the development of vaccines through cellular manipulation rather than animal experimentation.

Nevertheless, this historical overview of vaccines and immunization since Jenner's great cowpox discovery suggests that we can anticipate several of the key issues that could hinder and complicate the future of vaccinology. Clearly, without adequate funding and fluid funding mechanisms, vaccine shortages will persist, and lives throughout the world will remain at risk. Closely linked are the issues of vaccine safety and the strict maintenance of sterilization standards. Even as these have improved greatly over time, the fact that vaccines are biological agents often makes them much more difficult than drugs to produce. Jenner and his peers faced this problem, and history has shown that the production of safe, efficacious vaccines will require persistent vigilance. Although antivaccinationists are still often portrayed as an annoying thorn in the side of medical progress, their concerns for safety and willingness to perform the duty of civic oversight has had some positive effects, especially in terms of popular health education.

As this paper has shown, there are important continuities in the history of vaccines and immunization. There have been shifts as well; unfortunately, one of the most pronounced has been the divestment of public agencies in vaccine research and production. If we could match the enormous scientific strides of the twentieth century with the political and economic investments of the nineteenth century, the world's citizens might be much healthier.

In closing, we suggest that Americans take advantage of the flu shortage hysteria of fall 2004 to learn from the historical record. We need to transform our anxieties and energies into concrete steps to ensure a comprehensive vaccine supply in 2005 and beyond. It would be exceedingly foolish to squander one of preventive medicine's greatest assets because of a neglected public health system and an inability to adequately coordinate market forces and regulatory demands with basic health needs.

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