2019

The Vaccine Race in the 21st Century

Ana Santos Rutschman
Saint Louis University School of Law, ana.rutschman@slu.edu

DRAFT (please direct comments to ana.rutschman@slu.edu)
Forthcoming in Arizona L. Rev 61:4

THE VACCINE RACE IN THE 21ST CENTURY

Ana Santos Rutschman[1]

In a world in which infectious diseases are spreading increasingly faster, the development of new human vaccines remains a priority in biopharmaceutical innovation. Legal scholars have addressed different aspects of vaccine regulation and administration, but less attention has been paid to the role of laws governing innovation during the stages of research and development (R&D) of vaccines.

This Article explores the race to develop new vaccines from its beginnings through the early 21st century, with a particular focus on the progressively pervasive role of intellectual property in governing vaccine innovation. It describes the insufficiencies of current innovation regimes in promoting socially desirable levels of vaccine R&D, particularly in the case of emerging pathogens, a phenomenon that is at odds with public health needs.

Moreover, the Article identifies transactional inefficiencies affecting the licensure of vaccine technology. In order to address this problem, the Article argues for adoption of a technology-specific solution, and proposes a narrowly construed "take-and-pay" regime based on liability rules, enabling access to vaccine technology by follow-on innovators.

TABLE OF CONTENTS

[1] Assistant Professor of Law, Saint Louis University School of Law. S.J.D., LL.M., Duke Law School. For helpful insights and comments, I would also like to thank Heather Bednarek, Sarah Burstein, Greer Donley, Roger Ford, Rob Gatter, Hank Greeley, Sam Halabi, Tabrez Ibrahim, Camilla Hrdy, Dmitry Karshtedt, Mark Lemley, Aisling McMahon, Laura Pedraza-Fariña, Govind Persad, Nicholson Price, Anya Prince, Sarah Rajec, Josh Sarnoff, Andres Sawicki, Jake Sherkow, Cathay Smith, Liza Vertinsky, Helen Yu and Patti Zettler. I am also grateful to the participants at the IP Scholars Conference at Berkeley Law, Health Law Scholars Workshop at Saint Louis University, Faculty Colloquium at Emory University School of Law, IP Scholars Roundtable at Texas A&M University School of Law, Public Health Conference at Pontificia Universidad Javeriana of Bogotá, Bio Lawlapalooza at Stanford Law School, Manzo Series at DePaul University College of Law, Health Law Professors Conference at Loyola University of Chicago School of Law, and the Junior IP Scholars Workshops at Northwestern University Pritzker School of Law, William & Mary Law School and the Law School at the University of Copenhagen. I also thank Dr. Stanley Plotkin and Dr. Irene Graham for their assistance with the scientific aspects of the Article.

INTRODUCTION

Vaccines[2] are among the most cost-effective ways of promoting public health.[3] In addition to preventing or lessening the impact of infectious diseases,[4] vaccines have been shown to significantly decrease disability and inequity within health systems.[5]

Yet, and in spite of the increasing burden posed by infectious diseases in the U.S. and abroad, the market for vaccines targeting emerging pathogens[6] is often considered unprofitable.[7] Globally, very few private companies are currently engaged in vaccine research and development (R&D),[8] and the public sector lacks the capacity to fully develop and manufacture new vaccines

[2] The World Health Organization defines vaccines as "a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and 'remember' it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters." WORLD HEALTH ORG., VACCINES, http://www.who.int/topics/vaccines/en/.

[3] See e.g. Vanessa Rémy et al., *Vaccination: The Cornerstone of an Efficient Healthcare System*, 3 JOURNAL MARK. ACCESS HEALTH POLICY 27041 (2015) (estimating that, over time, the diphtheria, tetanus, and pertussis (DTP) vaccine has saved the U.S. health system $23.6 billion).

[4] The Article focuses on vaccines targeting infectious diseases, which form the bulk of diseases for which there are either approved vaccines or ongoing vaccine R&D. Examples of this type of disease include influenza, whooping cough, measles and HIV/AIDS. See Stanley A. Plotkin et al., *Establishing a Global Vaccine-Development Fund*, NEW ENGLAND J. MED. 297, 298 (Jul. 23, 2015) (listing vaccine-preventable diseases). Additional categories of ongoing vaccine R&D tend to rely on technology that is not yet fully developed, and consequently there is little to no information about the underlying economics and market configuration for those vaccines. For instance, no DNA vaccines have been approved by the U.S. Food and Drug Administration or by any other regulatory entity in the world. Similarly, technology currently used in the development of cancer vaccine candidates is still in its infancy (the currently available human papillomavirus (HPV) vaccine is considered by many scientists to be a simpler type of vaccine technology than cancer vaccines proper). See also generally Chunqing Guo et al., *Therapeutic Cancer Vaccines: Past, Present and Future*, 119 ADV. CANCER RES. 421 (2013) (summarizing R&D on therapeutic cancer vaccines); Lei Li et al., *The Future of Human DNA Vaccines*, 162 J. BIOTECHNOL. 171 (2013) (summarizing R&D on DNA vaccines).

[5] See generally F. E. André et al., *Vaccination Greatly Reduces Disease, Disability, Death and Inequity Worldwide*, 86 BULL. WORLD HEALTH ORG. 140 (2008).

[6] The Article further zeroes in on vaccines targeting neglected diseases, such as infectious diseases in the Zika and Ebola families, as well as vaccines targeting known pathogens for which no vaccine has entered the market, such as cytomegalovirus. See *infra*, notes 156 and 223 and accompanying text.

[7] See *infra*, note 212.

[8] See *infra*, note 87 and accompanying text.

on its own.[9] Over time, the rates of new or innovative vaccines[10] entering the market have sharply declined.[11]

Market forces are at odds with the public health need to promote innovative vaccine R&D, and the consequences of the current underinvestment in vaccine innovation may prove dire.[12] This paradox has long been recognized.[13] But so far it has not been comprehensively analyzed in connection with the legal regimes designed to foster R&D, facilitate transfers of technology among innovators and disseminate innovative goods. This Article fills that gap, identifying a disconnect between the reliance on proprietary rights as the default mechanism to incentivize technical innovation and the specific characteristics of vaccine R&D. In order to address this disconnect, the Article argues that legal interventions are needed to curb the overly proprietary contours of the regimes governing vaccine R&D in the U.S.,[14] without eliminating patent-driven models of vaccine R&D competition.

The Article looks at the evolution of vaccine technologies[15] through the progression of vaccine R&D in a race-like format through time. The initial race(s) to develop vaccines took place in lightly regulated environments that posed minimal constraints to innovative practices.[16] Together with a series of scientific breakthroughs and a spike in funding for vaccine R&D, the 20th century ushered in a golden age of vaccine innovation.[17] This boom in vaccine R&D resulted in the development of multiple vaccines which have contributed to reducing mortality and managing morbidity caused by a broad range of infectious diseases.[18] Examples include meningitis, hepatitis

[9] See *infra*, note 166 and accompanying text.

[10] The Article uses the concept of innovation in a broad sense, and without attempting to provide formal metrics to measure innovation (or inventive levels) in the field of vaccine R&D. Rather, the Article looks at innovation from the perspective of continued and follow-on activity leading to the discovery, production and commercialization of new vaccine technologies. As seen in Part II, the development or availability of a new vaccine or vaccine technology might not represent a true leap forward in scientific terms, and as such an increase in number of approved vaccines might not directly correlate with an increase in vaccine innovation from a scientific perspective. It should be noted that assessing innovation in the field of vaccine R&D presents particular difficulties. Data from the 20th century on vaccine R&D is incomplete and fragmented. Regulatory data on vaccine approvals is often unreliable, and sometimes plainly inaccurate. See e.g. HOYT, *infra* note 75. Nevertheless, even imperfect data can be used as a general proxy to identify industry and market trends in vaccine development, manufacturing and commercialization.

[11] *Infra*, Part I.B.

[12] See e.g. Julia Belluz, *4 Reasons Disease Outbreaks Are Erupting Around the World*, VOX (May 31, 2016), https://www.vox.com/ 2016/5/31/11638796/why-there-are-more-infectious-disease-outbreaks (noting that the numbers of outbreaks attributable to infectious diseases has been on the rise).

[13] See U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, A REVIEW OF SELECTED FEDERAL VACCINE AND IMMUNIZATION POLICIES, BASED ON CASE STUDIES OF PNEUMOCOCCAL VACCINE [hereinafter OTA Report], (1979).

[14] See FINANCING VACCINES IN THE 21ST CENTURY: ASSURING ACCESS AND AVAILABILITY (hereinafter FINANCING VACCINES), National Academies Press (2003), at 116 (noting that vaccines developed in the U.S. have contributed to as much as two thirds of global vaccine innovation in recent decades).

[15] By "vaccine technology" this Article refers to any components and processes used in the development, manufacturing and delivery of vaccines. Examples include proteins and atomizers (nasal sprays).

[16] *Infra*, Part I.A.

[17] *Infra*, Part I.B.

[18] *Id*.

B, influenza, tuberculosis, measles, mumps and rubella—diseases against which patient populations in the U.S. are now routinely vaccinated.[19]

As progressively stricter regulatory frameworks for vaccine R&D and administration were imposed, vaccine manufacturers began exiting the market.[20] Manufacturer attrition chronologically overlaps with a decrease in the number of vaccines entering the market in the second half of the 20th century. This coincides with the period in which the race to produce new vaccines also became a race to patent vaccine technology, although the Article does not claim a correlation between the two phenomena.[21]

In the 21st century, increasingly larger public-private partnerships operating in the vaccine R&D space have sought to counter the prevailing market forces and finance expenditures in vaccine technologies. While subscribing to the view that the rise of public-private partnerships is contributing to the promotion of vaccine R&D, the Article notes that this trend alone is unlikely to introduce the necessary systemic reforms needed to address the vaccine development paradox. It suggests, however, that collaborative approaches like the ones embodied by these partnerships might point the way towards more collaborative approaches to vaccine development.[22]

In addition to problems pertaining to R&D incentives, the Article identifies at least one instance in which reliance on the patent system as the default mechanism to incentivize vaccine innovation has resulted in inefficient transactional practices between vaccine manufacturers. Through a short case study on the cytomegalovirus vaccine,[23] the Article illustrates the problem technology dispersion, which takes place when different patent-protected elements needed to make a vaccine are scattered among non-cooperative firms.[24] This practice, if replicated in other contexts, can unnecessarily raise transaction costs and potentially delays or inhibits innovation.[25]

The Article argues that the problems posed by technology dispersion, together with the severity of the lack of market incentives for vaccine innovation, justify the need for technology-specific interventions.[26] Specifically, it proposes and describes a framework for the creation of a "take-and-pay" regime applicable solely to vaccine-related technologies (or subsets thereof) covered by proprietary rights. Under such a regime, inspired by the use of liability rules,[27] follow-on innovators wishing to use patent-protected vaccine technology for R&D purposes would not have to bargain with the patent holder. Rather, they would pay the rights holder for the use of an invention, according to a pre-established compensatory framework.[28] This solution, which goes

[19] See Stanley A. Plotkin et al., *Establishing a Global Vaccine-Development Fund*, *supra* note 4. See also AMERICAN ASS'N PEDIATRICS, RED BOOK: REPORT OF THE COMMITTEE ON INFECTIOUS DISEASES, KIMBERLY ET AL. (Eds.) (2015) (providing an authoritative discussion on vaccination and prevention of pediatric infectious diseases).

[20] *Infra*, Part I.B.

[21] *Infra*, Part I.C.

[22] *Id.*

[23] *Infra*, Part I.B.

[24] *Infra*, Part III.A.

[25] Interview with Dr. Stanley Plotkin, *infra* note 78.

[26] *Infra*, Part III.B.

[27] See *infra*, note 260 and accompanying text.

[28] See *infra*, note 291 and accompanying text.

against the traditional logics of proprietary rights, nonetheless preserves the original entitlement of the patent holder,[29] and is justified by broader social justice goals.

The Article proceeds as follows. Part I traces the progression of the vaccine race through time: initially, as a race against disease in an R&D environment where law and regulations played little to no role; then, as a market-based race within an expanding legal architecture; and, finally, as an idiosyncratic variant of the patent race. Part II focuses on the vaccine development paradox. It explores the characteristics that make vaccine development unique, originating a "valley of death" for vaccine R&D: a systemic inability to push vaccine technology through the R&D pipeline and bring it to market. It then identifies transaction problems associated with vaccine R&D, in the form of technology dispersion in a fragmented market. Part III argues that additional solutions to promote vaccine R&D are still needed, and that they should be technology-specific, such as the proposed adoption of a narrowly construed liability regime to foster follow-on innovation in vaccine R&D. A brief conclusion follows.

I. THE RACE TO DEVELOP NEW VACCINES

The idea of vaccine R&D as a race is usually equated with competing efforts to develop new vaccines throughout the 20th century.[30] The apex of this race is often portrayed as the golden age of the 1940-1960s, when the expansion of the biopharmaceutical industry in the U.S. and interlinked scientific breakthroughs resulted in the development of numerous vaccines.[31]

However, these descriptive frameworks do not fully capture the ever-changing nature of vaccine development. In particular, these accounts need to be supplemented from two angles. First, from an innovation theory perspective, it is incomplete to look at vaccine R&D as a 20th-century endeavor that has decayed into an unprofitable venture in the early 21st century. Rather, it has always been heterogeneously characterized by evolving moving parts, which include shifting institutional arrangements, varying market forces, and nuances in public health imperatives and discourses. And second, from the viewpoint of law as a catalyst for innovation, different periods of our race to develop new vaccines have been differently shaped by a plurality of factors. These include legal incentives, regulatory frameworks, and interactions between collaborative partnerships, as well as our notions of proprietary elements of science.

Bringing these components into legal scholarship focused on innovation regimes is relevant, and not merely for historical or descriptive accuracy. As vaccine R&D plummets and vaccine-preventable diseases increase their toll,[32] understanding the many facets and variables of vaccine races should inform our current policies and decision-making processes. To that effect, Part I of the Article shows how the development of vaccines took the shape of a race at distinct levels: first, as a race against pathogens in a largely unregulated environment; later, as a race to overcome regulatory barriers to market; and, finally, as a patent-driven race.

---

[29] "Entitlement" is used here in connection with legal theory scholarship on liability versus property rules, and without speaking to the ongoing debate about the nature of patents. See *infra* note 263 and accompanying text.

[30] See e.g. MEREDITH WADMAN, THE VACCINE RACE, VIKING (2017) (situating the vaccine race as a phenomenon that took place in the mid- to late-20th century).

[31] *Infra*, Part I.B.

[32] *Supra*, note 12.

A. THE FIRST VACCINE RACE

The first vaccine in history[33] is usually credited to Edward Jenner, an 18th-century British country doctor who took an interest in smallpox.[34] Smallpox, a now-eradicated infectious disease, is one of the most feared and lethal diseases in human history.[35] It ravaged populations across the globe for over three millennia, causing disfiguring skin lesions and killing an estimated 300 to 500 million people in the 20th century alone.[36]

In 1796, Jenner developed a rudimentary version of a smallpox vaccine[37] by taking a sample of an animal virus related to smallpox and introducing it into the system of a healthy eight-year old boy.[38] This triggered an immune reaction, the first to be documented by scientific parameters.[39] It was the first step towards eradication of smallpox through vaccination, a goal that would eventually be achieved in 1980.[40]

Jenner's actions earned him a place in history as the inventor of the first vaccine. In reality, however, Jenner did not actually invent vaccination.[41] The theory that Jenner tested experientially—that infection with an animal poxvirus triggered immunity to smallpox in

---

[33] See Edward Jenner, *An Inquiry into the Causes and Effects of the Variolae Vaccinae, A Disease Discovered in Some of the Western Countries of England, Particularly Gloucestershire, and Known by the Name of The Cow Pox*, London (1798) (reporting what is commonly regarded as the first vaccination experiment in history). See also Stanley Plotkin, *History of Vaccination*, Proceedings of the National Academy of Sciences of the United States of America, 12283, 12284 (2014) (listing Jenner's smallpox vaccine as the first human vaccine).

[34] See generally Andrea A. Rusnock, *Historical Context and the Roots of Jenner's Discovery*, 12 HUMAN VACCINES & IMMUNOTHERAPEUTICS 2025 (2016); E. Ashworth Underwood, *Edward Jenner, Benjamin Waterhouse and the Introduction of Vaccination into the United States*, 163 NATURE 823 (1949). See also CTR. FOR DISEASE CONTROL & PREVENTION, SMALLPOX (describing the main characteristics of the variola virus, which causes smallpox), https://www.cdc.gov/smallpox/index.html.

[35] See D. A. HENDERSON, SMALLPOX: THE DEATH OF A DISEASE, PROMETHEUS (2009), at 19 (noting that "no disease has killed so many hundreds of millions of people nor so frequently altered the course of history"). See generally DONALD R. HOPKINS, THE GREATEST KILLER: SMALLPOX IN HISTORY, Chicago University Press (2002).

[36] See Catherine Thèves et al., *The Rediscovery of Smallpox*, 20 CLINICAL MICROBIOLOGY & INFECTION

210, 212 (2014) (noting that, although smallpox (variola major) had an average mortality of 30%, in cases of hemorrhagic smallpox, mortality rates were higher than 97% in unvaccinated populations).

[37] The term vaccine was coined a few years after Jenner's experiment. See, e.g., Derrick Baxby, *Edward Jenner's Inquiry After 200 Years*, 318 THE BRITISH MEDICAL JOURNAL 390 (1999).

[38] See Jenner, *An Inquiry*, *supra* note 33.

[39] *Id*. Jenner documented further experiments and submitted a systematic account of the results to the Royal Society of London.

[40] HENDERSON, SMALLPOX, *supra* note 35.

[41] See Cary P. Gross & Kent A. Sepkowitz, *The Myth of the Medical Breakthrough: Smallpox, Vaccination, and Jenner Reconsidered*, 3 INT. J. INFECT. DIS. 54 (1998). See also MICHAEL KINCH, BETWEEN HOPE AND FEAR: A HISTORY OF VACCINES AND HUMAN IMMUNITY, PEGASUS (2018)

humans—was common knowledge at the time.[42] Farmers in the area were familiar with the theory, and at least one had tried applying it years before Jenner.[43]

Even the broader idea of immunization through contact with an attenuated form of a virus had been in practice for centuries before Jenner, from medieval China to early seventeenth-century Turkey, and probably even earlier.[44]

Nevertheless, Jenner's scientific reporting of his experiments with the smallpox vaccine set in motion a chain of events that enabled vaccine R&D to grow as a field. From the perspective of innovation diffusion, Jenner's reporting also laid the foundation for the first race towards large-scale production of vaccines. Because Jenner's vaccine was not patented,[45] anyone with minimal skill in the field was able to replicate it. But while proprietary rights over the vaccine itself did not constitute a barrier to market entrance, the availability of the raw materials needed to make the vaccine was limited. Competition thus arose in the form of a race to gather samples of vaccine material. The first vaccine race began as a race to biological materials, and a largely unregulated one.[46]

Nowhere was this more evident than in America. Unlike in Britain, there was no naturally occurring cowpox in America.[47] Doctors wishing to manufacture a vaccine had to import samples,[48] a process that increased the cost and time of making vaccines, at a time when outbreaks were constant. As several doctors tapped into their contacts in England, one of them moved ahead in this first vaccine race. Benjamin Waterhouse, one of the most prominent physicians of the time,[49] was able to obtain vaccine material through his friendship with a doctor and philanthropist based in London, who sent him "thread impregnated with vaccine matter."[50] Waterhouse became the first person to test the smallpox vaccine in America,[51] and shortly thereafter the first innovator who attempted to acquire proprietary rights over a vaccine. As one commentator has put it:

---

[42] See Susan Brink, *What's The Real Story About The Milkmaid And The Smallpox Vaccine?*, NPR (Feb.1, 2018), https://www.npr.org/sections/goatsandsoda/2018/02/01/582370199/whats-the-real-story-about-the-milkmaid-and-the-smallpox-vaccine (noting that, although popular legend has it that Jenner heard of immunity conferred by cowpox from a milkmaid, the more likely scenario is that he was familiar with inoculation experiments performed earlier by country doctors nearby).

[43] See Patrick J. Pead, *Benjamin Jesty: The First Vaccinator Revealed*, 9554 LANCET 2202 (2006) (describing how Jesty immunized his family against smallpox in 1774).

[44] Inoculation, the practice of removing organic matter from an infected patient and applying it subcutaneously to a healthy patient, has been documented throughout history. See Arthur Boylston, *The Origins of Inoculation*, 105 J. R. SOC. MED. 309 (2012) (describing early forms of inoculation in China and Turkey).

[45] Both Britain and the colonies were at this point granting patents. Jenner did not apply for one.

[46] There was no vaccine regulation at the federal level until 1902. See *infra*, note 61. Between 1822 and 1902, some states attempted to regulate vaccines (minimally). See generally, JOHN DUFFY, THE SANITARIANS, University of Illinois Press (1992).

[47] ARTHUR ALLEN, VACCINE, W.W. Norton & Co (2007), at 50.

[48] *Id.*, at 50.

[49] Waterhouse had co-founded Harvard Medical School in the 1780s and was generally regarded as one of the leading physicians of the time. See Robert H. Halsey, *How the President, Thomas Jefferson, and Doctor Benjamin Waterhouse Established Vaccination as a Public Health Procedure*, N.Y. (1936).

[50] ALLEN, at 50.

[51] *Id.*, *ib.*

> Waterhouse's first blunder would perhaps seem natural in today's patent-crazy biomedical community: he tried to extract generous terms for himself from physicians in exchange for sharing the material. In a September 1800 proposal sent to Dr. Lyman Spalding of Portsmouth, NH, Waterhouse demanded exclusive rights to supply the vaccine—plus a quarter of Spalding's fees."[52]

Waterhouse's approach more closely resembles the competitive nature of today's R&D process than that of his time. It is the first instance of the vaccine race taking proprietary contours, complete with a royalty-based licensing scheme. In the next section, the Article shows how a property-centric approach to vaccine development became the hallmark of the golden age of vaccine R&D in the 20th century. In the early 19th century, however, that approach did not last long. After a few months, other doctors were able to have vaccine material shipped from England.[53] With competition again unfettered by proprietary claims, a proto-vaccine manufacturing industry emerged on the East Coast.[54]

Vaccine farms, as production units were called, operated in conditions that would be described today as unsanitary at best.[55] As vaccination became increasingly common, there were sporadic attempts to regulate the race to produce new vaccines, which soon took place at industrial levels. In 1812, a national Vaccine Agent was appointed,[56] and the following year Congress passed the first Vaccine Act, in an attempt to promote vaccination against smallpox.[57] It took however a major public health crisis for more comprehensive federal legislation on vaccines to be enacted.[58] In 1901, fatal incidents[59] linked to the use of contaminated vaccines in Saint Louis and Camden, NJ, prompted the industry to lobby for federal legislation on vaccine manufacturing and distribution.[60] The following year, Congress passed the Act of 1902, later called the Biologics

---

[52] *Id.*, *ib.*

[53] *Id.*, *ib.*

[54] *Id.*, at 75.

[55] See e.g. Walter Reed, *What Credence Should be Given to the Statements of Those Who Claim to Furnish Vaccine Lymph Free of Bacteria*, 5 JOURNAL OF PRACTICAL MEDICINE 532, 532-34 (1985) (reporting the presence of bacteria in samples obtained from needles used in vaccine production by six of the largest vaccine manufacturers of the time).

[56] S.L. KOTAR & J.E. GESSLER, SMALLPOX: A HISTORY, McFarland (2013) at 91.

[57] "An Act to Encourage Vaccination" (Feb. 27, 1813). The 1813 Act was repealed in 1822. See generally DONALD R. OPKINS, PRINCES AND PEASANTS: SMALLPOX IN HISTORY, University of Chicago Press (1983). In 1832, Congress passed the Indian Vaccination Act, appropriating $12,000 to extend smallpox vaccination to Native American populations.

[58] Until the early 20th century, the states that took an interest in vaccines tended to be primarily concerned with the legality of compulsory vaccination. See e.g. *Jacobson v. Massachusetts*, 197 US 11 (1905) (upholding the authority of the Board of Health of Cambridge, MA, to mandate vaccination during a smallpox outbreak).

[59] See Ross E. DeHovitz, *The 1901 St Louis Incident: The First Modern Medical Disaster*, 133(6) PEDIATRICS 964 (2014). See also David E. Lilienfeld, *The First Pharmacoepidemiologic Investigations: National Drug Safety Policy in the United States, 1901-1902*, 51 PERSPECT. BIOL. MED. 188 (2008).

[60] See Terry S. Coleman, *Early Developments in Biologics Regulation*, 71 FOOD & DRUG LAW JOURNAL 544, 551 (2016) (noting the role of pharmaceutical companies in lobbying for regulation of vaccines at the federal level).

Control Act,[61] which offered a regulatory framework for vaccine manufacturing.[62] This and other laws enacted throughout the 20th century ushered in a period that is often called the golden age of vaccine innovation—large-scale R&D in a highly competitive environment, resulting in multiple new vaccines entering the market and greatly reducing the burden of many vaccine-preventable diseases.

B. Golden Age and Decline of Vaccine Innovation

For over a century, smallpox was the only disease for which there was a vaccine in America.[63] The R&D landscape then changed significantly through the early and mid-20th century, when additional types of vaccine technology were developed.[64]

The early smallpox vaccine had paved the way for live vaccines (made with a weakened pathogen).[65] Three other types of vaccines followed: toxoid vaccines (made with a toxin produced by bacteria)[66] targeting diseases like diphtheria and tetanus; inactivated vaccines (made with a killed pathogen),[67] targeting diseases like hepatitis A and the flu; and biosynthetic vaccines (containing man-made substances)[68] targeting diseases like hepatitis B and meningitis.[69]

The quick development of multiple new vaccines in the first half of the 20th century has led commentators to talk about a "golden age of vaccines," with some distinguishing between a first golden period in the early 1900s and a second one following World War I and the Great Depression.[70] Irrespective of historical categorizations, for the purposes of this Article the relevant facts are that there was a spur in vaccine R&D in the early to mid-20th century, as further detailed below; that vaccine innovation occurred in the context of a highly competitive market;[71] and that

---

[61] Pub. L. No. 57-244, 32 Stat. 728 (1902) (repealed 1944). Today vaccines are largely regulated by the Public Health Service Act, Ch. 288, 37 Stat. 309 (1912).

[62] See generally Coleman, *Early Developments in Biologics Regulation*, *supra* note 60.

[63] Allen, at 15-16.

[64] See WIPO report, at 16 (listing the major types of vaccines currently under development).

[65] Other examples of live vaccines include Pasteur's rabies vaccine and the measles, mumps, and rubella (MMR) vaccine.

[66] World Health Org., Toxoid Vaccines, http://vaccine-safety-training.org/toxoid-vaccines.html.

[67] World Health Org., inactivated whole-cell (killed antigen) vaccines, http://vaccine-safety-training.org/inactivated-whole-cell-vaccines.html.

[68] This group includes different sub-groups of vaccines. See U.S. Nat'l. Inst. Health, Vaccines (Immunizations) – Overview, https://medlineplus.gov/ency/article/002024.htm; World Health Org., subunit vaccines, http://vaccine-safety-training.org/subunit-vaccines.html. Some commentators address subunit, recombinant, polysaccharide, and conjugate vaccines separately. See e.g. U.S. Dept. of Health and Human Services, Vaccine Types, https://www.vaccines.gov/basics/types/index.html.

[69] Today, there two additional types of vaccines, both at the experimental level (and hence not commercially available): DNA vaccines and recombinant vector vaccines; see Nat'l. Inst. Health Allergy & Infectious diseases, Vaccine Types, https://www.niaid.nih.gov/research/vaccine-types (last accessed June 2019).

[70] OTA Report, *supra* note 13, at 149. The terminology is not uniform; see e.g. Isabel Delany et al., *Vaccines for the 21st Century*, 6 EMBO Mol. Med. 708, 708 (2014) (situating the first golden period in the early 20th century and the second one from the 1950s onwards).

[71] See Fig. 2.

R&D translated into dozens of new vaccines entering the market over the course of a few decades.[72]

In 1902—the year in which Congress enacted what would become known as the Biologics Act[73]—there were no licensed vaccine manufacturers in the U.S., and no licensed vaccines.[74] Between 1903 and 1916, 38 establishments were granted a license to manufacture vaccines, and dozens of vaccines gained regulatory approval.[75] After a slight drop in the 1920s,[76] vaccine R&D and licensure rose to record numbers that remain unmatched in history: by 1940, there were 52 vaccine manufacturers, and the number of licensed vaccines commercialized in the U.S. is estimated to have surpassed 60.[77]

In the 1950s and 1960s, vaccine manufacturers, both American and foreign, began exiting the U.S. market, citing the soaring costs of obtaining regulatory approval for vaccines[78] and, above all, concerns with "unpredictable liability risks" associated with vaccine administration in the U.S.[79] This phenomenon prompted systemic market attrition, with as many as 12 manufacturers

---

[72] See Fig. 1.

[73] *Infra,* note 61.

[74] OTA Report, *supra* note 13, at 149. See Figs. 1 and 2. The lack of licensed vaccines was merely a corollary of the lack of a regulatory framework for vaccine licensure. Vaccines were nonetheless in use before that, and there was a vaccine industry in the U.S., clustered in the Philadelphia area, as early as the late 19th century. ALLEN, *supra* note XX, at 75.

[75] OTA Report, *ib.* There are discrepancies in the number of licensed vaccines between the study conducted by the now-defunct Office of Technology Assessment (OTA) in 1979 and later analyses relying on more accurate data. The official number of new "vaccine products" indicated in the OTA study for the 1903-1916 period is 367. An authoritative 2012 study estimated that the number of "significant vaccine introductions" during this period was actually 27. See KENDALL HOYT, LONG SHOT: VACCINES FOR NATIONAL DEFENSE, Harvard University Press (2012), 180-183. The discrepancy is likely due to inconsistencies in the recording of regulatory data by a plethora of agents in a changing institutional environment. HOYT, at 38 (noting that "each time regulatory responsibility changed hands, original approval dates were either lost or reentered with a more recent date, creating the false impression that there was a spate of innovation with each transition.")

[76] Between 1916 and 1918, several European vaccine manufacturers exited the U.S. market. OTA Report, *supra* note 13, at 149 (noting that vaccine licensure increased for nearly a decade after the end of WWI). According to the Report, the number of licensed vaccine manufacturers decreased from 40 to 33 between 1927 and 1931. *Id.*

[77] The official number of new vaccines listed in the OTA Report is 607. See OTA Report, at 149. However, as noted in note 75, this number is likely inflated. Hoyt's 2012 study reports that there was a total of 64 new vaccine products introduced in the U.S. market between 1903 and 1940. See HOYT, *supra* note 75, 180-186.

[78] Interview with Dr. Stanley Plotkin, leading developer of the standard rubella vaccine, author of the leading medical book on vaccines, and consultant to Sanofi, a large pharmaceutical company with a strong presence in the U.S. vaccine market through its vaccine division, Sanofi-Pasteur, which is the world's largest vaccine (noting that "today there are fewer manufacturers of vaccines of the regulatory requirements that were added from the 60s onwards). (Interview on file with author). See STANLEY A. PLOTKIN, M.D., NATIONAL FOUNDATION FOR INFECTIOUS DISEASES, http://www.nfid.org/awards/plotkin.pdf. See also SANOFI-PASTEUR, OUR VACCINES, https://www.sanofipasteur.com/en/immunization-essentials/#preventable. See also OTA Report, at 5.

[79] OTA Report, at 5. See e.g. *Givens v. Lederle Laboratories*, 556 F.2d 1341 (5th Cir. 1977); *Reyes v. Wyeth Laboratories*, 98 F.2d 1264 (5th Cir. 1974); *Davis v. Wyeth Laboratories*, 399 F.2d 121, 131 (9th Cir.1968) (collectively holding that vaccine manufacturers must warn consumers directly of the risks associated with vaccine administration, eschewing the learned intermediary doctrine).

quitting vaccine R&D in a single decade.[80] In 1967, there were 26 manufacturers in the U.S.; in 1980, the number had decreased to 17.[81]

In 1986, Congress passed the National Childhood Vaccine Injury Act, establishing a no-fault compensation program for vaccine-related injuries funded by an excise tax.[82] In return, vaccine manufacturers received broad immunity from tort-based claims for vaccine-related injuries.[83] The Act established, inter alia, that manufacturers would not be liable "in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."[84]

The Act was an overt policy attempt to curb vaccine-related tort litigation and stabilize the vaccine market.[85] It failed on the second account,[86] as it was unable to stop or reduce the rate of market attrition among manufacturers. By 2003, there were four left in the U.S. market.[87]

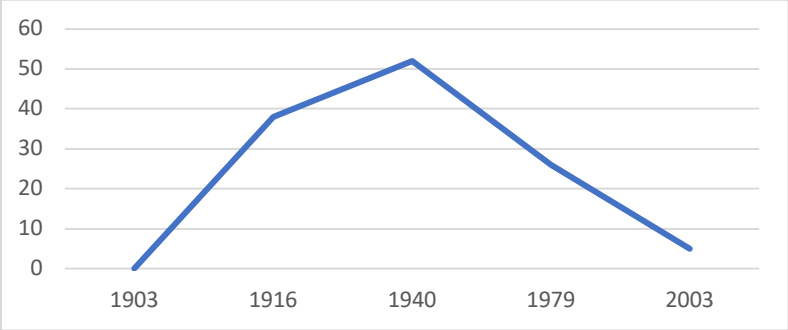


Figure 1: Number of Licensed Vaccine Manufacturers in the U.S.

Part II looks in greater detail at the specific characteristics of vaccine R&D, which likely were on of the contributing causes of the manufacturer exodus even after a legal intervention

[80] See F. M. Scherer, *An Industrial Organization Perspective on the Influenza Vaccine Shortage*, 28 MANAGERIAL & DECISION ECONOMICS 393, 394 (2007).

[81] FINANCING VACCINES, *supra* note 14, at 121.

[82] 42 U.S.C. §300aa–21-§300aa–23.

[83] See *Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 223 (2011) (framing the Act as a *quid pro quo* between the pursuit of market stability and the need to guarantee compensation for vaccine-related injuries).

[84] 42 U.S.C. § 300aa–22(b)(1).

[85] *Bruesewitz v. Wyeth LLC*, at 223 (2011) (describing the purpose of the Act as "to stabilize a vaccine market adversely affected by an increase in vaccine-related tort litigation and to facilitate compensation to claimants who found pursuing legitimate vaccine-inflicted injuries too costly and difficult").

[86] For a comprehensive analysis of the impact of the Act, including its other shortcoming, see Efthimios Parasidis, *Recalibrating Vaccination Laws*, XX B.U. L. REV. 2153 (2018).

[87] See ALLEN, VACCINE, *supra* note 47, at 75, (noting that by 2003 "four companies together produce[d] nearly all of the standard childhood vaccines. Five vaccines recommended for administration in the United States during 2003 were obtained from only one producer, and most of the others had only two producers (e.g. injectable influenza vaccine) or three sources." See also Jon Cohen, *U.S. Vaccine Supply Falls Seriously Short*, SCIENCE 1998, 1998 (Mar. 15, 2002).

designed to lessen the burden posed by tort litigation.[88] But it is worthwhile to note here that, from the perspective of R&D players,[89] the phenomenon of market consolidation coincided with the end of the golden age.[90] Other parameters, like the declining number of licensed vaccines, appear to corroborate the idea that the mechanics of vaccine innovation have changed. Consider the number of products available to consumers: as of 2018 there are 80 licensed vaccines in the U.S., several of which target the same disease and use the same vaccine technology.[91] The rate of introduction of vaccines targeting new diseases, or applying new vaccine technology to a given disease, has slowed as well.[92]

The golden age of vaccine innovation was thus characterized by numerous companies flocking to market in the early to mid-20th century, and the resulting introduction of important new vaccines.[93] There are, however, additional characteristics of the vaccine race that extend beyond the spike in the number of vaccine manufacturers, or the number of new vaccines gaining regulatory approval.[94] One of the most significant is the element of competition among vaccine developers: no other example embodies the race-like qualities of vaccine development better than polio R&D, which involved less-than-friendly competition between scientists using different types of vaccine technology.[95]

Polio is a disease that targets primarily children, potentially leading to permanent paralysis or death.[96] It was widely feared across mid-20th-century America,[97] infecting tens of thousands of people every year.[98] Against the backdrop of such a public health need for an effective vaccine, the competition among the scientists developing the leading vaccine candidates (as well as the institutions supporting them) has been portrayed as a war.[99]

---

[88] *Supra*, note 79.

[89] The private-sector entities involved in vaccine R&D tend to double as vaccine manufacturers. This is why the number of vaccine manufacturers is a good proxy for vaccine innovation from an R&D perspective. The exception to the double role of researcher/manufacturer is the public sector, which tends to be involved in the early stages of vaccine R&D, but lacks manufacturing capacity.

[90] See e.g. OTA Report, *supra* note 13, at 149. Using a corrected data set regarding the number of new vaccines entering the U.S. market, Hoyt agrees that vaccine innovation declined throughout the second half of the 20th century. See HOYT, *supra* note 75.

[91] See U.S. FOOD & DRUG ADMIN., VACCINES LICENSED FOR USE IN THE UNITED STATES, https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm (data last updated Mar. 29, 2018)

[92] See HISTORY OF VACCINES, TIMELINE, https://www.historyofvaccines.org/timeline.

[93] Drug R&D in general experienced a boom in the mid-20th century that came to a close towards the end of the century. See ROBERT RYDZEWSKI, REAL WORLD DRUG DISCOVERY, Elsevier (2008) at 5.

[94] *Infra*, Part II.B.

[95] Gilbert King, *Salk, Sabin and the Race Against Polio*, SMITHSONIAN MAGAZINE (Apr. 3, 2012) (noting that one of the leading vaccine candidates was a killed vaccine, while the other was a live, attenuated vaccine).

[96] See generally DAVID M. OSHINSKY, POLIO: AN AMERICAN STORY, Oxford University Press (2006); JANE S. SMITH, PATENTING THE SUN, William Morrow & Co. (1990); WORLD HEALTH ORG., POLIOMYELITIS (POLIO), http://www.who.int/topics/poliomyelitis/en/ (last accessed June 2019).

[97] See generally OSHINSKY, POLIO. See also PHILIP ROTH, NEMESIS, Houghton Mifflin Harcourt (2010) (capturing the anxiety produced by polio outbreaks in summertime).

[98] King, *supra* note 95 (reporting between 25,000 and 50,000 annual polio cases in the 1950s, and 3,000 child deaths in 1952 alone).

[99] See generally WADMAN, *supra* note 30.

Among other instances, clinical trials were performed on mentally ill children;[100] the scientist behind the winning vaccine candidate fought against randomized and blinded clinical trials;[101] competitors publicly thrashed one another over scientific reporting of polio research;[102] the vaccine that first emerged from this race received regulatory approval on the same day that its safety and efficacy was reported;[103] an antiseptic was added to this vaccine without being tested;[104] and one of the six licensed manufacturers did not follow the vaccine's specifications, infecting 40,000 people with polio, and killing or injuring several children.[105]

In the long term, this race did lead to the near-eradication of polio at a global level.[106] The public health impact of the first commercially available was such that the scientist who invented it, Jonas Salk, became a celebrity, and the vaccine became known as "the Salk vaccine."[107] If from the perspective of market competition the 1940s were the high point of the golden age of vaccines, polio R&D turned the 1950s into the apex of vaccine development as a race between opposing parties.

This carries important ramifications from the regulatory viewpoint. Heightened competition between vaccine developers accentuated the need for stricter regulations concerning vaccine development, testing and manufacturing. Shortly after the polio vaccine race, and on the heels of the thalidomide scandal,[108] the Food and Drug Administration (FDA) began regulating drugs much more strictly, requiring sponsors to demonstrate the efficacy of the drug in addition to its safety.[109] From an R&D perspective, the need to generate, collect and submit more data made drug development longer and more expensive.[110]

As FDA regulations became progressively stricter, and the regulatory review process as a whole became costlier than before, and direct competition between vaccine developers in a shrinking market brought to the forefront another key element driving vaccine innovation:

---

[100] ALLEN, VACCINE, *supra* note 47, at 185.

[101] Placebo-controlled trials did eventually take place. See Marcia L. Meldrum, *The Salk Polio Vaccine Field Trials of 1954*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS, EZEKIAL J. EMANUEL ET AL. (EDITORS), at 63-65. What we would today define as informed consent was however lacking; see ALLEN, at 161.

[102] ALLEN, at 187.

[103] Tara Haelle, *Polio Vaccine Found "Safe And Effective" 60 Years Ago: What Would Salk Think Today?*, FORBES (Apr. 13, 2015).

[104] *Id.*

[105] This became known as the Cutter Incident, and prompted the FDA to issue more stringent vaccine regulations. See generally PAUL A. OFFIT, THE CUTTER INCIDENT: HOW AMERICA'S FIRST POLIO VACCINE LED TO THE GROWING VACCINE CRISIS, Yale University Press (2005).

[106] *Supra*, note 96. See also WORLD HEALTH ORG., 10 FACTS ON POLIO ERADICATION (2017) (noting a 99% reduction in polio rates), https://www.who.int/features/factfiles/polio/en/ (last accessed June 2019)

[107] ALLEN, VACCINE, *supra* note 47, at 187-88.

[108] See generally Neil Vargesson, *Thalidomide-Induced Teratogenesis: History and Mechanisms*, 105 BIRTH DEFECTS RES. 140 (2015). See also Geoff Watts, *Frances Oldham Kelsey*, 386 LANCET 1334 (2015) (memorializing the FDA scientist who reviewed the thalidomide application and questioned the safety of the drug).

[109] In an attempt to guarantee higher standards for drugs in general, the Kefauver–Harris Amendments of 1962 introduced the requirement that, in addition to demonstrating safety, drug sponsors must also demonstrate efficacy as a condition of regulatory approval, a two-pronged regime that endures to our days. See Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50*, 367 NEW ENG. J. MED., 1481 (2012).

[110] See *supra*, note 13.

proprietary rights over emerging vaccine technologies, to which the Article turns in the following section.

The golden age of vaccines was, therefore, a multi-level race that quickly turned into a competition-centric process, crystalizing non-collaborative models of R&D as the paradigm of vaccine development. As discussed in Part II.C, this competition-driven approach has left an imprint in the form of siloed vaccine R&D that is still felt today.

C. "PATENTING THE SUN:" VACCINE DEVELOPMENT AND THE EMERGENCE OF PROPRIETARY RIGHTS

On the episode of the CBS documentary *See it Now* broadcast on April 12, 1955, Edward R. Murrow interviewed Jonas Salk, the developer of the first commercially available polio vaccine in the world.[111] Murrow asked: "Who owns the patent on this vaccine?" Salk answered: "Well, the people, I would say. There is no patent." On footage preserved on YouTube, one can still see Salk take an infinitesimal pause and then add: "Could you patent the sun?"[112]

Salk's words have become famous.[113] They stand for the idea that basic science should not be fenced in by intellectual property barriers, and that basic scientific tools should be freely available to all.

In fact, as articulated by Salk, the idea of the impossibility of patenting the sun presciently spells out the boundaries of eligible subject matter in biotechnology, as set by the Supreme Court twenty-five years later, in *Diamond v. Chakrabarty*.[114] In examining the patentability of living microorganisms, the Court observed that Congressional intent had been to craft patent subject matter broadly, to include "anything under the sun that is made by man."[115] Patent law protects man-made inventions, but not laws of nature, physical phenomena, and abstract ideas.[116] Earlier Supreme Court case law had foreshadowed this idea: in *Funk Bros.*, the Court explicitly declared unpatentable "the heat of the sun," which belonged to the category of things that should remain "free to all men and reserved exclusively to none."[117]

Writing for the majority in *Chakrabarty*, Justice Burger went on to note that patent law's exclusionary principle would have prevented Einstein from having any intellectual property rights over $E=mc^2$ or Newton, over the law of universal gravitation.[118] In this sense, Jonas Salk was correct: it is impossible to patent the sun, and it is undesirable from a policy perspective to lock-

[111] See generally OSHINSKY, *supra* note 96.

[112] Jessica Kaluza-Klein, *Could You Patent the Sun?*, YOUTUBE (Mar. 22, 2013), https://www.youtube.com/watch?v=AEH_M3O1mtM (last accessed May 2019).

[113] See SMITH, *supra* note 97, at 13.

[114] 447 U.S. 303 (1980).

[115] *Id.*, at 309.

[116] *Id.*, at 303.

[117] *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). The other examples mentioned by Justice Douglas in *Funk Bros.* are (what today we would define as naturally occurring) bacteria, electricity and properties of metals. *Id., ib.*

[118] *Id.*, *ib.*

in the building blocks of scientific research. But vaccines are not akin to the sun, and Salk's analogy fails on every other account.[119]

The unpatentable element behind vaccine innovation is the idea of triggering immunity against a specific disease, an idea that, as seen in Part I.A, preceded by centuries the invention of the first vaccine by Edward Jenner. But a host of different components of any given vaccine, as well as combinations thereof, are patent-eligible,[120] as long as they meet the statutory requirements of novelty, non-obviousness and usefulness.[121] Examples of these components include the main components of a vaccine, like antigens;[122] inactive or residual ingredients like stabilizers[123] (e.g. sugars); adjuvants[124] to enhance immune responses (e.g. aluminum salts); manufacturing processes;[125] the delivery method and the delivery device.[126]

If at the time of Jenner's vaccine proprietary claims over vaccine material (like Waterhouse's) stood out as aberrant, the golden age of vaccine innovation made prospective reliance on patents the norm.[127] In fact, contrary to what his statements on Murrow's show might imply, Jonas Salk himself had actually contemplated patenting the polio vaccine.[128] Lawyers at the National Foundation for Infantile Paralysis, which funded Salk's research, assessed the patentability of the polio vaccine and concluded that it failed to meet the statutory requirement of novelty.[129] The John Enders lab at the Children's Medical Center in Boston had grown poliovirus in 1949, and Salk used their technique to develop his vaccine three years later.[130] Other scientists had made additional discoveries that Salk had openly relied on,[131] and for these reasons it was determined that "there was nothing to patent."[132]

---

[119] Salk was not the only scientist voicing his (at least theoretical) opposition to certain patents. Enrico Fermi, a Nobel Prize-winner physicist, was known for going a step further and declaring that scientists should not have any proprietary rights over their inventions. See generally GINO SEGRÈ & BETTINA HOERLIN, THE POPE OF PHYSICS: ENRICO FERMI AND THE BIRTH OF THE ATOMIC AGE, Henry Holt & Co. (2016).

[120] See 35 U.S.C. § 101.

[121] Respectively, 35 U.S.C. § 102, § 103 and § 101.

[122] Antigens are substances that induce immune responses from the body. See CTR. FOR DISEASE CONTROL AND PREVENTION, VACCINES & IMMUNIZATION GLOSSARY, https://www.cdc.gov/vaccines/terms/glossary.html (last accessed June 2019).

[123] See e.g. Carl Burke & David Volkin, WO1999012568A1 ("Stabilizers Containing Recombinant Human Serum Albumin for Live Virus Vaccines").

[124] See e.g. Eric M. Bonnem et al., US5679356A ("Use of GM-CSF as a Vaccine Adjuvant").

[125] See e.g. Majid Mehtali et al., CA2604330C ("Process of Manufacturing Viral Vaccines in Suspension Avian Embryonic Derived Stem Cell Lines").

[126] See e.g. Eric James Wall, US7670314B2 ("Injection Device for Administering a Vaccine").

[127] *Infra*, fig. 1.

[128] OSHINSKY, AMERICAN STORY, *supra* note 96, at 63-65.

[129] SMITH, PATENTING THE SUN, *supra* note 96.

[130] ALLEN, VACCINE, *supra* note 47, at 196-97.

[131] That was the case, for instance, of Dorothy Horstmann at Yale. See Heather A. Carleton, *Putting Together the Pieces of Polio: How Dorothy Horstmann Helped Solve the Puzzle*, 84 YALE J BIOL. MED. 83, 84-85 (2011).

[132] ALLEN, at 197.

In the 1980s and 1990s, Salk conducted R&D in the field of HIV and did not object to patenting the results.[133] A patent search reveals several HIV vaccine-related patents that were granted to Salk and a co-inventor.[134]

This is not to say that inventors should not be awarded patents for meritorious contributions to vaccine R&D.[135] But it illustrates the idea that patents have permeated the ethos of vaccine R&D. Empirical data supports the finding that this other aspect of the vaccine race—the race to patents—started in the mid-20th century. A study by the World Intellectual Property Organization (WIPO) has shown that the levels of patenting activity in the field of vaccines have steadily increased from the 1960s onwards.[136] The study identified 11,818 families[137] of patents or patent applications filed between the 1920s and the first decade of the 21st century,[138] with most of the filing activity (5,230 cases) concentrated in the U.S.[139]

WIPO analysts mined historical data from patent offices across the globe, gathering information on 11,569 first filings of patent-related vaccine applications.[140] While first filings are an imperfect measurement of actual inventiveness—as patent applications may be abandoned, rejected or reexamined[141]—they can be seen as an indicator that patents gradually become a relevant tool in vaccine R&D strategies. For instance, in 1955, the year Salk's polio vaccine was approved, there were 4 first fillings globally.[142] A decade later the number quintupled (20), and in 1985 it was up to 126.[143] In 1998, the number of worldwide first filings went over 500, and in 2007 it surpassed the 600-mark.[144] While there is no comprehensive dataset allowing us to infer a correlation between first filings and issued patents covering vaccine technology, an increase in

---

[133] Brian Palmer, *Jonas Salk: Good at Virology, Bad at Economics*, SLATE, http://www.slate.com/articles/technology/history_of_innovation/2014/04/the_real_reasons_jonas_salk_didn_t_patent_the_polio_vaccine.html (Apr. 13, 2014).

[134] These patents were assigned to The Immune Response Corporation, which Salk co-founded. See e.g. U.S. Patent 5,256,767A (issued Oct. 26, 1993) (covering retroviral antigens, as well as methods of production and preparation).

[135] The reasons behind the need for patents as an incentive mechanism in the specific field of vaccine R&D are discussed in Part II.

[136] WORLD INTELL. PROP. ORG., PATENT LANDSCAPE REPORT ON VACCINES FOR SELECTED INFECTIOUS DISEASES [hereinafter WIPO Report] (2012).

[137] Per WIPO terminology, a patent family is a "collection of published patent documents relating to the same invention, or to several inventions sharing a common aspect, that are published at different times in the same country or published in different countries or regions." WIPO, HANDBOOK ON INDUSTRIAL PROPERTY INFORMATION AND DOCUMENTATION: GLOSSARY OF TERMS CONCERNING INDUSTRIAL PROPERTY INFORMATION AND DOCUMENTATION (June 2013), at 8.1.18.

[138] WIPO Report, at 16.

[139] WIPO Report, at 22. Between 1921 and 2011, WIPO calculated that there were 5,230 first filings of vaccine-related patent applications in the U.S., as opposed to 1133 in China, 942 in the United Kingdom, 632 in Japan, 625 in Russia, and 449 in France. In the developing world, Brazil led the way with 75 first filings, followed by India with 69, and South Africa with 20.

[140] WIPO Report, at 25-26. The data collected by WIPO does not include numbers from countries that do not publish patent applications that are not granted. *Id.*, at 20. See also *infra*, note 147).

[141] Reexamination might lead to invalidation of the patent. See 35 U.S.C. § 321; 35 U.S.C. § 311.

[142] WIPO Report, at 25. All the 1955 filings took place in the U.S.

[143] *Id.*, at 25-26.

[144] *Id.*, at 26.

filing activity of this magnitude, and over such an extended period of time, seems to indicate that intellectual property became a systemic component of vaccine R&D in the late 20th century.

I used the raw data provided by WIPO to produce three graphics illustrating the upward trend in patents or patent applications covering innovation related to vaccine R&D. The first graph maps the evolution of global[145] first filings from the beginnings of the golden age of vaccine development to the end of the 2000s.[146]

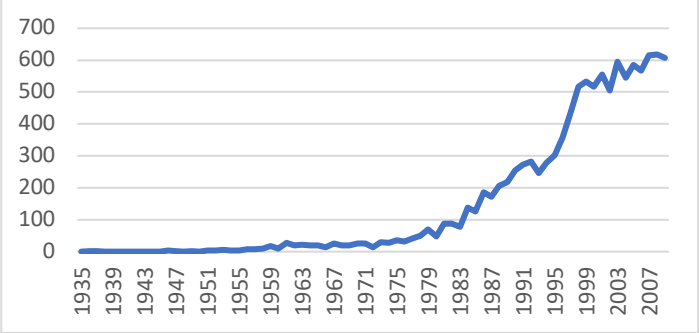
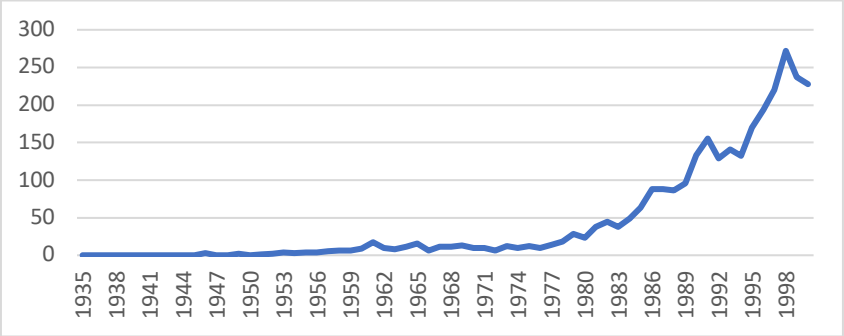


Figure 1: Number of worldwide first filings (1935-2009)

The second graph focuses on patents covering vaccine technology issued in the U.S. between 1935 and 2000. Until late November 2000, the U.S. Patent and Trademark Office did not publish patent applications.[147] Therefore, the data collected by WIPO until then encompasses only the number of vaccine-related patents granted in the U.S., but not the overall number of related patent applications, unlike in other countries. In the graphic below, I adjusted the information accordingly.



[145] A total of 57 countries reported patents or patent applications related to vaccine technology. *Id.*, at 25-26.

[146] 2009 being the last year for which there is reliable data on first filings in this area. See WIPO Report, at 20 (noting that data included in the WIPO study for the post-2009 period is incomplete due to an 18-month delay in the publication of patent applications).

[147] USPTO, *USPTO Will Begin Publishing Patent Applications*, Press Release 00-72 (Nov. 27, 2000), available at https://www.uspto.gov/about-us/news-updates/uspto-will-begin-publishing-patent-applications (last accessed May 2019). See 35 U.S.C. § 102 (b)(1)(A) (describing the publication requirement introduced by the Leahy-Smith America Invents Act).

Figure 2: Number of Vaccine Patents Granted by the USPTO (1935-2000)

The third graph combines vaccine-related patents that issued between 1935 and 2000 period in the U.S. with vaccine-related patents and patent applications filed in the U.S. between 2000 and 2009.[148]

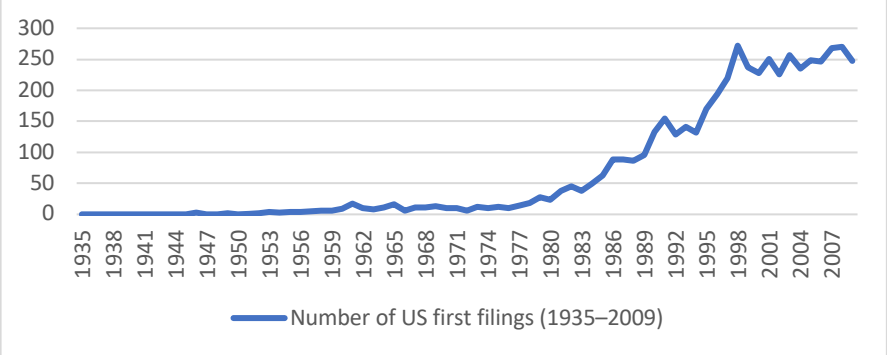


Figure 3: Number of U.S. First Filings Involving Vaccine Technology (1935-2009)

The evolution of patent grants and patent applications in the U.S. is consistent with global trends, with the absolute number of first filings consistently surpassing the aggregated volume of first filings in the rest of the world. In 1955, the year of the Salk vaccine, 4 vaccine patents were granted in the U.S. A decade later that number had quadrupled. By the mid-1970s, the Patent and Trademark Office was issuing an average of 12 vaccine-related patents a year. In the late 1980s, that number jumped to close to 90, and in the late 1990s it surpassed 200. From 200 onwards, when patent applications were added to issued patents, the number rose to the mid- to high-200s.

The emergence of intellectual property rights as part of the process of vaccine R&D is in line with the findings of literature on the role of patents in biopharmaceutical innovation.[149] But there is an additional layer that has so far remained unexplored. In the field of vaccines, the rise of patenting activity coincides with an actual decrease in the number of vaccine approvals in the U.S., as well as with the market consolidation caused by the sharp reduction in the number of vaccine manufacturers, as described in the previous section.

A comparison between these dimensions yields two initial insights. First, it suggests that it is unlikely that there might be a correlation between patenting activity and vaccine innovation, if we assess the latter by the number of new vaccines entering the market during a selected period of time. And second, while it does not prove that market concentration led to more aggressive patenting strategies, it does indicate that the shrinking number of vaccine manufacturers in the U.S. is highly engaged in patenting the results of vaccine R&D.

There are also a few limitations to the data presented above that raise additional questions worth further investigation. First, it is hard to discern any impact caused by the introduction of stricter vaccine regulations by the FDA in the early 1960s. The numbers of vaccine patents issued in the U.S. dipped the year after the regulations came into force (1963) and were not especially high during the following decade, but no conclusions can be drawn on the strength of this data

[148] WIPO Report, at 25-26.

[149] See e.g. Eisenberg, *infra* note 152.

alone. And second, the rise of patenting activity from the 1980s onwards coincides with the birth and boom of the biotech industry,[150] of which vaccine R&D is a sub-set. This phenomenon has undoubtedly left an imprint on the vaccine race, which the data presented above cannot fully capture.

Nevertheless, it is clear the race towards proprietary rights has become an important feature of vaccine R&D. This does not mean that vaccine innovation cannot take place outside patent-centric models of R&D. As Amy Kapczynski has demonstrated, there has been sustained R&D and considerable levels of innovation around the development of vaccines targeting the pandemic flu.[151]

But the salience of intellectual property mechanisms in vaccine innovation bears further exploring: as industry claims that patents are a sine qua non of biopharmaceutical R&D,[152] what are the consequences of a patent-based vaccine race? And if patents incentivize investment in costly and risky areas, what made vaccine R&D so appealing during the golden age, and what makes it a deterrent to investment today? The following section turns to these questions, examining the vaccine R&D process in greater detail, and placing both the structural features of vaccine markets and the role of vaccine patents into a broader context.

II. BARRIERS TO VACCINE DEVELOPMENT

Part I outlined the contours of the race to produce new vaccines. For decades, that race has resulted in diminishing vaccine innovation. In 2015, the Foundation for Vaccine Research compiled a list of categories of vaccine-preventable diseases for which there was no vaccine, or only a partially effective vaccine: the final count totaled 47 categories, including diseases like hepatitis C, HIV, universal influenza and Lyme disease.[153]

As detailed in the following sections, the reasons for the current lack of much-needed vaccines are manifold. In some cases, the problem is largely scientific: recall the examples of cancer vaccines or a universal flu vaccine, for which there are funded R&D projects, but that seems dependent on scientific breakthroughs that have yet to occur.[154]

In other cases, we lack vaccines for diseases for which promising R&D has stopped,[155] or because R&D has never taken place.[156] While these are two different scenarios, they are rooted in

---

[150] See generally SALLY SMITH HUGHES, GENENTECH: THE BEGINNINGS OF BIOTECH, University of Chicago Press (2011).

[151] Amy Kapczynski, *Order Without Intellectual Property Law: The Flu Network as a Case Study in Open Science*, 102 CORNELL L. REV. 1539 (2017). See also, WORLD HEALTH ORG., PANDEMIC INFLUENZA PREPAREDNESS FRAMEWORK (2011) (laying out the foundations for the sharing of flu viruses, as well as a benefit sharing regime).

[152] See e.g. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 346-47 (2007) (noting that the biopharmaceutical industry has "sung the praises" of patents as incentives to R&D).

[153] See Plotkin et al., *Establishing a Global Vaccine-Development Fund*, *supra* note 4, at 298 (noting that, for a minority of these categories, there were vaccines in advanced R&D stages, but that most of them were not in development).

[154] See *supra*, note 4 and accompanying text.

[155] That was the case with the leading Ebola Zika candidate before the 2014-15 outbreak, See *infra*, Part II.A.

[156] That was the case of Zika vaccines before the 2015-16 outbreaks. See generally Ana Santos Rutschman, *IP Preparedness for Outbreak Diseases*, 65 UCLA L. REV. 1200 (2018).

the same problem: vaccine R&D,[157] often described as an expensive and risky endeavor with limited markets to recoup costs,[158] is off-putting to funders and, by extension, ignored by (certain) research communities. These are the cases that concern this Article from now on, as they represent failures of legal and policy regimes aimed at promoting biopharmaceutical innovation.

Part II explores the reasons that make markets adverse to vaccine R&D. The first section introduces this phenomenon by contrasting it with the public health need for the development of both new and better vaccines. The following section focuses on the specific causes of failing R&D regimes for vaccines.

A. THE VACCINE DEVELOPMENT PARADOX

Vaccines both prevent disease[159] and reduce its burden.[160] They are widely considered highly cost-effective mechanisms that result in substantial savings to national health systems.[161] Yet, we lack vaccines for dozens of infectious diseases, many of which are currently on the rise.[162]

As the first vaccine-preventable diseases were eradicated in the 20th century, vaccine manufacturers exited the market en masse.[163] With the notable exception of a few existing vaccines,[164] the contemporary market for vaccines targeting emerging pathogens is often considered too small to attract substantial private investment,[165] and the public sector is generally

---

[157] As pertaining to vaccines targeting emerging pathogens, as noted above. See supra note 4.

[158] See *infra*, note 184 and accompanying text.

[159] See Walter A. Orenstein et al., *Contemporary Vaccine Challenges: Improving Global Health One Shot at a Time*, 253 SCIENCE TRANSLATIONAL MEDICINE 1, 1 (2014) (noting that vaccination approaches are generally superior to therapeutic interventions). See also Nathalie Largeron et al., *Role of Vaccination in the Sustainability of Healthcare Systems*, 3 JOURNAL MARK. ACCESS HEALTH POLICY 27043 (2015); FINANCING VACCINES, *supra* note 14, at 24.

[160] See André et al., *Vaccination Greatly Reduces Disease, Disability, Death and Inequity Worldwide*, *supra* note 5. See also FINANCING VACCINES, *supra* note 14, at 4.

[161] See Rémy et al., *Vaccination*, *supra* note 3 (estimating that routine administration of a single vaccine has saved the U.S. health system over USD 20 billion). The cost of epidemics has been estimated in the region of USD 600 billion over the course of ten years. See also FINANCING VACCINES, at 8 (noting that "vaccines provide a net long-term savings in health care costs").

[162] See Plotkin, *Establishing a Global Vaccine-Development Fund*, *supra* note 4. See also Katherine F. Smith et al., *Global Rise in Human Infectious Disease Outbreaks*, 11 J. R. SOC. INTERFACE 101 (2014); NPR, *Why Killer Viruses Are on the Rise*, https://www.npr.org/sections/goatsandsoda/2017/02/14/511227050/why-killer-viruses-are-on-the-rise.

[163] WORLD HEALTH ORG., VACCINE MARKET, http://www.who.int/immunization/programmes_systems/procurement/market/global_supply/en/ (noting that five multinational companies "that were the product of various mergers and acquisitions of pharmaceutical companies over the past decades" account for 80% of global vaccine sales).

[164] See Bourree Lam, *Vaccines Are Profitable, So What?*, ATLANTIC (Feb. 10, 2015) (noting that there are a few "blockbuster" vaccines on the market, such as the pneumococcal conjugate vaccine, which is one of the vaccines recommended by the Center for Disease Control and Prevention for all children under 2 years old). See also CTR. FOR DISEASE CONTROL AND PREVENTION, PNEUMOCOCCAL VACCINATION, https://www.cdc.gov/vaccines/vpd/pneumo/index.html (last accessed June 2019).

[165] See *A Smarter Jab*, THE ECONOMIST (Oct. 14, 2010) (calling vaccine R&D the "neglected corner of the drugs business, with old technology, little investment and abysmal profit margins"), https://www.economist.com/business/2010/10/14/a-smarter-jab (last accessed June 2019).

unable to carry vaccine R&D through the later stages of clinical development.[166] The dynamics of vaccine development are paradoxical, in that from a public health perspective they are valued highly, but from a market perspective they tend to be considered an unattractive investment, and thus relegated to the backburner of biopharmaceutical R&D.

Some commentators have pointed out that vaccine R&D is "not a priority for industry" because of the unlikelihood of return on investment.[167] At the same time, empirical evidence suggests that revenue generated by vaccines has been growing steadily since the turn of the century. In a study by PATH[168] for the Global Vaccine and Immunization Research Forum, the global vaccine market was estimated to be worth USD 6 billion in 2000; USD 17 billion in 2008; USD 28 billion in 2011; and USD 33 billion in 2014.[169] While this growth is encouraging, these numbers should be considered in perspective: a single blockbuster (non-vaccine) drug often generates a third or more of the overall revenue generated by vaccines. For instance, the highest-grossing drug in the world in recent years, a biologic sold under the brand name Humira, generated USD 18.4 billion in revenue in 2017 alone.[170] Rituxan, the second best-selling drug worldwide in the same year, generated USD 9.2 billion,[171] with several other biologic drugs in the USD 7-8 billion range.[172]

An especially problematic feature of R&D in the field of vaccines is that, even when there is funding available for initial R&D, the so-called "valley of death" is especially pronounced. The expression "valley of death" is commonly employed to describe the difficulty in transitioning from the early stages of R&D to the commercialization of a new technology, particularly in the realm of drug innovation (including vaccine innovation).[173] The valley of death typically begins at the

---

[166] Interview with Dr. Stanley Plotkin, supra note 78.

[167] See Rino Rapuoli et al., *The Intangible Value of Vaccination*, 297 SCIENCE 937, 937 (2002).

[168] PATH is a Seattle-based, non-profit organization formerly known as Program for Appropriate Technology in Health, which focuses on the promotion of "health equity" and "access to health." See PATH, https://www.path.org/about/.

[169] Amie Batson, GLOBAL VACCINE MARKET, PATH REPORT TO THE GLOBAL VACCINE AND IMMUNIZATION RESEARCH FORUM (Mar. 26, 2016) http://www.who.int/immunization/research/forums_and_initiatives/1_ABatson_Global_Vaccine_Market_gvirf16.pdf (last accessed May 2019).

[170] See Bob Herman, *Humira Sales Surpass $18 Billion*, AXIOS (Jan. 26, 2018), https://www.axios.com/humira-sales-surpass-18-billion-1516983676-980b4594-e31b-4f05-aea7-c99da6a2232b.html (last accessed May 2019). Humira is used in the treatment of inflammatory diseases, and is one of the best-selling drugs of all time. See Simon King, *The Best Selling Drugs of All Time; Humira Joins The Elite*, FORBES (Jan. 23, 2013), https://www.forbes.com/sites/simonking/2013/01/28/the-best-selling-drugs-of-all-time-humira-joins-the-elite/ (last accessed May 2019).

[171] See e.g. Alex Philippidis, *The Top 15 Best-Selling Drugs of 2017*, GENENGNEWS (2018) https://www.genengnews.com/a-lists/the-top-15-best-selling-drugs-of-2017/ (last accessed June 2019).

[172] *Id.*

[173] See Arti K. Rai et al., *Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery*, 8 YALE J. HEALTH POL'Y L. & ETHICS 53, 58 (2008) (defining the valley of death in biotechnology as the gap that "separates upstream research from downstream product"). Carol Mimura et al., *Perspective: Socially Responsible Licensing, Euclidean Innovation, and the Valley of Death*, 5 STAN. J. L. SCI. & POL'Y (2011), at 3 (noting that, in some R&D fields, gaps between initial research and deployment of a technology "are particularly wide, reflecting, for example, long research and development ("R&D") timelines, substantial required investments, and regulatory hurdles prior to commercialization"). See also COMM. ON ACCELERATING TECH TRANSITION, NAT'L RESEARCH COUNCIL, ACCELERATING TECHNOLOGY TRANSITION: BRIDGING THE VALLEY OF DEATH FOR MATERIALS AND PROCESSES IN DEFENSE SYSTEMS (2004) (exploring the valley of death in the military

end of preclinical R&D (research taking place before trials on human subjects begin). It encompasses the prolonged and costly stages of clinical development of a drug or vaccine (in the form of trials involving human subjects) and regulatory approval (submission of results and interaction with the FDA or similar regulatory agencies).[174]

In practice, this translates into the unavailability of fully developed and/or approved vaccines in situations in which preclinical R&D has occurred and has proven successful. An example of a recent valley of death involved Ebola R&D, which produced a viable vaccine candidate in the early 2000s.[175] A successful patent application for the vaccine was filed in 2003,[176] and two years later animal tests concluded, showing the vaccine candidate to be "highly efficacious."[177] From then on, however, the institution that developed the vaccine struggled to find a pharmaceutical company willing to start clinical development of the vaccine.[178] So great was the lack of interest—although this was the leading Ebola vaccine candidate in the world—that between 2005 and 2014 "[t]he vaccine sat on a shelf."[179] The valley of death seemingly[180] came to an end with the Ebola outbreak in West Africa in 2014, which prompted a race among dozens of private companies and public-private partnerships to develop different types of Ebola vaccines.[181]

From a public health perspective, vaccine R&D is thus often at odds with market forces: vaccines may prevent disease from spreading, but it often takes a potentially preventable health crisis, or decades of strain to public health systems, for vaccine R&D to attract funding and interest.[182]

---

innovation ecosystem, but also addressing cultural and sociological theories of innovation diffusion that explain difficulties in R&D and technology transfer).

[174] See Plotkin et al., *supra* note NEW ENG. J. MED., at 297 (defining the valley of death for vaccines as "the critical steps after good preclinical data have been obtained, comprising manufacture to Food and Drug Administration standards, a phase 1 clinical trial, and proof of concept in terms of protective immune responses. This support would permit efficacy assessment to begin").

[175] Rutschman, *IP Preparedness*, *supra* note 156.

[176] Recombinant Vesicular Stomatitis Virus Vaccines for Viral Hemorrhagic Fevers, Can. Patent No. WO 2004/011488 A2 (filed July 28, 2003).

[177] See Stephen M. Jones et al., *Live Attenuated Recombinant Vaccine Protects Nonhuman Primates Against Ebola and Marburg Viruses*, 11 NATURE MED. 786 (2005).

[178] Rutschman, *IP Preparedness*, *supra* note 156, at 1221-1222.

[179] Denise Grady, *Ebola Vaccine, Ready for Test, Sat on the Shelf*, N.Y. TIMES (Oct. 23, 2014).

[180] As of mid-2018, there are multiple vaccine candidates in the later stages of clinical development, but no vaccine has yet been approved by the FDA. See Yves Lévy, *Prevention of Ebola Virus Disease Through Vaccination: Where We Are in 2018*, XX LANCET 1 (Aug. 10, 2018). As clinical development of Ebola vaccines takes place, further outbreaks have occurred. See WORLD HEALTH ORG., EBOLA SITUATION REPORTS: DEMOCRATIC REPUBLIC OF THE CONGO (Aug. 17, 2018) (reporting the latest of the post-2014 Ebola outbreaks), http://www.who.int/csr/don/17-august-2018-ebola-drc/en/.

[181] Rutschman, *IP Preparedness*, *supra* note 156, 1224-1231.

[182] See e.g. Mark R. Schleiss, *Cytomegalovirus Vaccines Under Clinical Development*, 2 J. VIRUS ERAD. 198, 198 (2016) (noting that there is no approved vaccine for cytomegalovirus, which for decades has been known to cause heightened rates of morbidity and mortality among certain subsets of patient populations, which include HIV-affected patients).

While the phenomenon of the valley of death is not exclusive to vaccine R&D,[183] valleys of death for vaccines tend to be magnified by a confluence of scientific, economic and legal or regulatory factors, to which the Article now turns.

B. SPECIFICITIES OF VACCINE R&D

The vaccine market is often described as unprofitable.[184] As noted above, the size of the market is a fraction of the markets for other types of pharmaceuticals.[185] This is due to a host of factors, which result directly or indirectly from the unique characteristics of vaccines.

To begin with, vaccines differ from so-called conventional drugs, which are made of small molecules that are chemically synthesized.[186] Vaccines are a subset of biologics,[187] a category of large-molecule, structurally more complex drugs, made in living cells. This inherent complexity renders biologics more difficult and substantially more expensive to manufacture than other types of drugs.[188] As a consequence, from the perspective of would-be competitors, biologics cannot easily be replicated,[189] in sharp contrast with conventional drugs, which are reasonably easy to reverse-engineer, enabling generic competitors to produce relatively inexpensive copies.

Until very recently, the possibility of competition in the field of biologics was further diminished by the lack of a regulatory pathway for the approval of cheaper versions of biologics, commonly known as biosimilars.[190] In 1984, the Hatch-Waxman Act created an approval

---

[183] See Arti K. Rai et al., *Pathways Across the Valley of Death*, *supra*, note 173 and accompanying text.

[184] See *A Smarter Jab*, supra note 165.

[185] WORLD HEALTH ORG., VACCINE MARKET, http://www.who.int/immunization/programmes_systems/procurement/market/en/.

[186] See generally, INTRODUCTION TO BIOLOGICAL AND SMALL MOLECULE DRUG RESEARCH AND DEVELOPMENT: THEORY AND CASE STUDIES, C. ROBIN GANELLIN (ED.), Elsevier (2013).

[187] See 42 U.S.C. § 262(i)(1) (defining a biologic for regulatory purposes as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."). See also Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, 1(4) BIOTECHNOL HEALTHC. 24 (2004).

[188] See W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023 (2016). The cost of developing a new vaccine has been estimated to range from USD 135 million to USD 500 million, and in some cases may be significantly higher. See Stanley Plotkin et al., *The Complexity and Cost of Vaccine Manufacturing – An Overview*, 35 VACCINE 4064 (2017). The time it takes to develop a new vaccine has been estimated in the neighborhood of 15 years. *Id.* The costs of building vaccine manufacturing facilities alone are also high, having been estimated to exceed USD 30 million. See Henry G. Grabowski & John Vernon, *The Search for New Vaccines: The Effects of the Vaccines for Children Program*, AEI Press (1997), at 27.

[189] See e.g. Marie E. Csete & John C. Doyle, *Reverse Engineering of Biological Complexity*, 295 SCIENCE 1664 (2002).

[190] See 42 U.S.C. § 262 (i)(2), which defines a biosimilar in relation to the reference biologic as being "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and presenting "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." In addition to biosimilars, there is a pathway for FDA to approve interchangeable biologic products, which will in theory compete with brand name biologics. See 42 U.S.C. § 262 (i)(3), defining an interchangeable product as one that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." As of late August 2018, the FDA has

mechanism for generic versions of small-molecule drugs.[191] But it was not until 2009, with the Biologics Price Competition and Innovation Act, that a regulatory pathway was created for sponsors of biosimilars to bring applications to the FDA.[192]

The lack of a regulatory mechanism allowing second-comers to compete with name brand biologics, together with structural complexity and difficulties in reverse-engineering biologics, help explain why the market for biologics has (so far) fewer players and is more concentrated than markets for conventional drugs. As biologics, vaccine markets are affected by these problems. Furthermore, in addition to differing from conventional drugs, vaccines also differ from other biologics, in ways that further shrink the number of players willing to enter the market.

One or two doses of a vaccine are often enough to generate life- or long-term immunity. Other drugs, including some of the current best-selling biologics, require much longer courses of treatment, generating more revenue.[193] Certain vaccine markets (especially in the developing world) present additional problems that are less significant for other drugs. Vaccines lose potency if exposed to heat or certain temperature variations, and a cold chain needs to be maintained at all times when vaccines are shipped to remote markets.[194]

As mentioned above, it is also problematic to accurately calculate the economic impact of vaccines on health systems. There are ways to do it, although they are not uniform. For example, the Institute of Medicine of the U.S. National Academies looks at the "protective efficacy, disease incidence, disease outcomes, and costs associated" with the use of a given vaccine.[195] Some entities, which measure the market in terms of sales of vaccines,[196] factor in monetary revenue but do not take into account the intangible value of vaccines—elements like the number of epidemics prevented and deaths averted.[197] This enhances the vaccine development paradox, as economic metrics may well underrepresent the public health value of vaccines, and in turn perpetuate the image of vaccine markets as unappealing to private investment.

Another peculiarity in the field of vaccines relates to the prominent role that the military has played in R&D from the mid-20th century onwards.[198] Infectious diseases caused by pathogens that are not endemic to the U.S. pose threats to service members deployed abroad, prompting the military to be an important initiator of research on these pathogens, as well as a frequent co-

---

approved 12 biosimilars, but no interchangeable products. See U.S. FOOD & DRUG ADMIN., BIOSIMILAR PRODUCT INFORMATION, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm

[191] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98- 417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355(j) and in scattered sections of the U.S. Code).

[192] Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119, 804 (2010) (codified as amended in scattered sections of the U.S. Code). See also 42 U.S.C. § 262(k) (laying out the framework for the licensure of biosimilar or interchangeable products.)

[193] Patricia M. Danzon et al., *Vaccine Supply: A Cross- National Perspective*, 24 HEALTH AFFAIRS 706, 707 (2005) ("The longer the efficacy [of a vaccine], the smaller the demand.")

[194] See generally John Lloyd & James Cheyne, *The Origins of the Vaccine Cold Chain and a Glimpse of the Future*, 35 VACCINE 2115 (2017).

[195] See FINANCING VACCINES, *supra* note 14, at 3.

[196] Batson, *supra* note 169.

[197] Rapuoli, *supra* note 167.

[198] See generally HOYT, LONG SHOT, HOYT, *supra* note 75.

developer of early-stage vaccine technology.[199] Examples of successful vaccine R&D in which the U.S. military was involved range from Yellow Fever to Zika, including a once-licensed Lyme disease vaccine, as well as ongoing work on an HIV vaccine candidate.[200] As these examples illustrate, many of the vaccines developed by the military become of use to the U.S. civil population.

From 1962 onwards, the U.S. military has co-developed a quarter of all licensed vaccines.[201] However, funding for military R&D on naturally acquired infectious diseases has sharply decreased.[202] The decrease is attributable a diversion of resources towards military R&D on bioterrorism agents,[203] magnified by a recent decrease in available funding for public-sector research in general.[204]

In the case of bioterrorism preparedness, vaccines play a prominent strategic role. They have been described as the "only practical means of protection" against biological weapons,[205] and as a consequence the U.S. military has been involved in the development of vaccines targeting agents like anthrax, the plague and smallpox.[206] Nevertheless, vaccines against bioterrorism agents do not significantly expand the size of the U.S. vaccine market: even with renewed interest in (and funding available for) the development of medical countermeasures[207] since 2001,[208] national stockpiles for this particular types of vaccine are currently insufficient to meet demand in the case of a bioterror attack.[209]

These features help explain why vaccine markets present unique challenges. Taken together with the factors surveyed in Part I–rising costs associated with regulatory review,[210] and

---

[199] *Id*.. See also Col. Kenneth E. Hall, *The Dangerous Decline in the US Military's Infectious-Disease Vaccine Program*, AIR & SPACE POWER JOURNAL (Spring 2011), at 103-104 (explaining why the military is institutionally well placed to co-develop vaccines).

[200] U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND, MILITARY INFECTIOUS DISEASES RESEARCH PROGRAM (MIDRP), http://mrmc.amedd.army.mil/index.cfm?pageid=medical_r_and_d.midrp.overview.

[201] RESEARCH AMERICA, DOD: THE U.S. COMMITMENT TO GLOBAL HEALTH R&D, https://www.researchamerica.org/sites/default/files/uploads/DoDFactsheet.pdf.

[202] See generally Hall, *The Dangerous Decline*, *supra* note 199, at 102.

[203] *Id.* See also Ali S. Khan & David A. Ashford, *Ready or Not—Preparedness for Bioterrorism*, 345 NEW ENG. J. MED. 287 (2001).

[204] See Jeffrey Mervis, *Data Check: Federal Share of Basic Research Hits New Low*, 355 SCIENCE 1005, 1005 (2017).

[205] Gregory A. Poland et al., *New Vaccine Development*, 324 BMJ 1315, 1317 (2002).

[206] CTR. DISEASE CONTROL & PREVENTION, BIOTERRORISM AGENTS/DISEASES, https://emergency.cdc.gov/agent/agentlist-category.asp. See also Philip K. Russell, *Vaccines in Civilian Defense Against Bioterrorism*, 5 EMERG. INFECT. DIS. 531 (1999).

[207] U.S. FOOD & DRUG ADMIN., WHAT ARE MEDICAL COUNTERMEASURES?, https://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/aboutmcmi/ucm431268.htm (listing vaccines, among others, as "that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, or a naturally occurring emerging disease").

[208] See Oliver Grundmann, *The Current State of Bioterrorist Attack Surveillance and Preparedness in the US*, 7 RISK MANAG. HEALTH POLICY 177 (2014).

[209] Russell, *supra* note 206, at 532. See also Cheryl Pellerin, *The ABCs of Battling Bioterrorism*, MIT TECH. REV. (May 9, 2001).

[210] Interview with Dr. Plotkin, *supra* note 78.

concerns with liability[211]–they also help explain the sharp consolidation of the market for vaccine manufacturers in the second half of the 20th century.

To further place vaccines in context, consider the following graph depicting the number of new drugs approved by the FDA since 2000 (with FDA approval being the threshold for market entrance, looking at vaccine approvals versus other drugs):

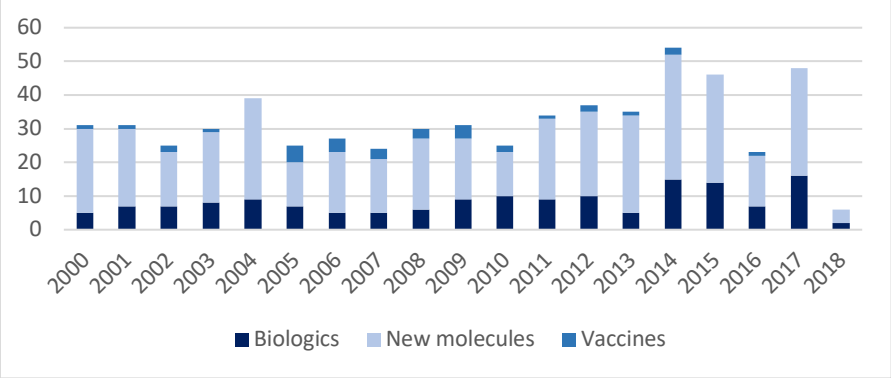


Figure 4: FDA Drug Approvals 2000-2018[212]

Between 2000 and 2017,[213] the FDA approved 32 new vaccines. This translates into an average of 1.8 vaccine approvals per year from 2000 onwards, although the period between 2005 and 2009 inclusive stands out as abnormally dynamic, with 19 approvals (an average of 3.8 approvals per year). The maximum number of approvals in a single year was five (2005), followed by four (2006, 2009), and three (2007, 2008). Between 2010 and 2017, the average number of FDA approvals dropped to one a year (eight vaccine approvals over a span of eight years), with no more than two approvals in a single year (2010, 2012, 2014). On three occasions, no new vaccines entered the market (2004, 2015, 2017).

While FDA approval and subsequent market entrance are not good proxies for market size, these numbers—seen in conjunction with revenue streams[214] and other data–provide yet another insight into the relative configuration of the vaccine market in the early 21st century.

III. Rethinking Normative Approaches to Foster Vaccine R&D

Having surveyed both the characteristics of the vaccine race and the specificities of vaccine R&D, the Article now focuses on the interplay between the later stages of vaccine R&D and the legal regime that is routinely seen as the default locus for incentivizing scientific and technical innovation—the patent system. Part III looks beyond the incentives-inducing dimension of intellectual property to consider the detrimental effects that the existence of intellectual property rights may at the transactional level in the context of vaccine R&D.

---

[211] *Supra* note 79 and accompanying text.

[212] Adapted from Laura DeFrancesco, *Drug Pipeline: 1Q18*, 5 Nature Biotech. 386 (May 9, 2018) and from U.S. Food & Drug Admin., Vaccines Licensed for Use in the United States, https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

[213] Full numbers for 2018 are not yet available.

[214] See *supra* note 169 and accompanying text.

A striking feature of vaccine R&D[215] is that it involves relatively simple technology. For instance, consider the case of the Zika vaccine developed during the 2015-16 outbreak:[216] making use of existing vaccine technology targeting a different pathogen in the Zika family, Army scientists were able to develop a vaccine candidate in just a few months.[217] That vaccine candidate, at the time considered the most promising in the world, failed not due to scientific or technological reasons, but because of dwindling interest from the private sector once the Army attempted to transfer rights over the vaccine to a single pharmaceutical company.[218] Similarly, the problems with the Ebola vaccine candidate mentioned in Part II.A were not of scientific or technological nature: the vaccine was created years before the severe outbreak of 2014-16, only to meet profound lack of interest from commercial manufacturers until the outbreak occurred. Even then, the problems that surrounded the later stages of vaccine R&D were transactional and patent-related:[219] a small company, unwilling to engage in R&D, held the rights[220] over the vaccine and delayed transfer of the vaccine technology until a striking a financially advantageous deal with a large company.[221] The delay was especially problematic as streams of funding triggered by the outbreak quickly began shrinking.[222]

Transactional problems in vaccine R&D also occur outside the context of outbreaks. The following section explores a particular embodiment of transactional inefficiencies in the form of dispersion of vaccine technology. The case study focuses on a common virus in the herpes family for which all vaccine components currently exist—but no approved vaccine. Part III.B then makes the case that transactional inefficiencies like the ones illustrated by the case study should be addressed through technology-specific legal interventions. Part III.C outlines the contours of such an intervention, in the form of a take-and-pay regime for vaccine components.

A. Technology Fragmentation in Vaccine R&D

As seen in Part I.B, patents have become an integral part of the ethos of vaccine races, but are insufficient to guarantee adequate investment in vaccine R&D.

The reliance on proprietary rights as the drivers of vaccine innovation raises an additional question: what role do they play when vaccine technology is scattered among different parties in the market? In other words, intellectual property is often thought of as an incentives mechanism, a conduit to stimulate R&D, but what happens when vaccine R&D actually takes place within the framework of proprietary rights?

---

[215] See *supra* note 157 and accompanying text.

[216] Kaiser Family Found., The 2015-2016 Zika Outbreak, https://www.kff.org/infographic/2015-2016-zika-outbreak/ (providing a timeline of the outbreak) (last accessed June 2019).

[217] Ana Santos Rutschman, *Vaccine Licensure in the Public Interest: Lessons from the Development of the U.S. Army Zika Vaccine*, 127 Yale L.J. F. 651, 654-655 (2018).

[218] *Id.*, at . See also

[219] See Rutschman, *IP Preparedness*, s*upra* note 156, 1244-1248 (describing the transactional issues surrounding licensure of Ebola vaccine candidates during the 2014-16 outbreak).

[220] The company, NewLink, had licensed the vaccine for USD 205,000. *Id.*, at 1247.

[221] NewLink received USD 30 million for the transfer of intellectual property surrounding the vaccine candidate to Merck, with an additional USD 20 million to be paid when clinical trials began. *Id., ib.*

[222] *Id.*

As a way of exploring these questions, the Article now introduces a case that illustrates the drawbacks of reliance on proprietary regimes in the specific scenario of vaccine R&D. The case involves R&D on vaccines targeting cytomegalovirus (CMV), a herpesvirus that infects more than half of adults by age 40.[223] In most cases, infection by CMV is asymptomatic or results in mild symptoms like fever or fatigue, but it can produce devastating effects and/or death on populations with weakened immune systems, including HIV-positive populations, as well as fetuses and newborns.[224]

As of mid-2018, there is no approved CMV vaccine.[225] There is, however, research being conducted in the U.S. on multiple types of vaccine candidates,[226] and different vaccine technologies have undergone clinical trials.[227] The leading expert on the field of vaccine development has described the R&D landscape as follows:

> The difficulty (…) is that to make a perfect vaccine, we need 3 elements and each of those is being developed by different entities. If we could put together three of the elements: a gB (glycoprotein B), a Pentamer, and pp65 [a protein], then we would have a CMV vaccine. It's not a simple matter to combine those things and to go through the process of manufacturing and to make sure they are all compatible. Getting people together and getting collaboration is the issue. I've been working with the various manufacturers and am involved in many of the projects. Sanofi (Sanofi Pasteur) is the manufacturer that sponsored the three successful studies with the gB candidate in Alabama, Cincinnati, and London. The problem with gB is that the antibodies don't last long enough, which can be solved by using an adjuvant, and Glaxo (GlaxoSmithKline) has good adjuvants.[228]

This description exemplifies a problem associated with management of goods protected by different bundles of proprietary rights.

Scholarship on resource management drew attention early on to the problems posed by the absence of property rights.[229] In a commons, understood as an unregulated space open to all, a "tragedy of the commons" occurs when unregulated use leads to over-depletion of resources. In Garrett Hardin's classic example, in a pasture open to any and all herdsmen, over-grazing will

---

[223] CTR. FOR DISEASE CONTROL AND PREVENTION, CYTOMEGALOVIRUS (CMV) AND CONGENITAL CMV INFECTION, https://www.cdc.gov/cmv/index.html.

[224] See e.g. Sheetal Manicklal et al., *The "Silent" Global Burden of Congenital Cytomegalovirus*, 26 CLINICAL MICROBIOLOGY REVIEWS 86 (2013). See also Schleiss, *supra* note 182.

[225] K. M. Anderhom et al., *Cytomegalovirus Vaccines: Current Status and Future Prospects*, 76 DRUGS 1625 (2017).

[226] *Id.*

[227] *Id.*

[228] NAT'L CMV FOUNDATION, DR. STANLEY PLOTKIN TALKS CMV VACCINE RESEARCH, https://www.nationalcmv.org/resources/blog/july-2016/dr-stanley-plotkin-talks-cmv-vaccine-research.

[229] See Garrett Hardin, *The Tragedy of the Commons*, 162 SCIENCE 1243 (1968).

eventually occur.[230] In cases similar to this, property rights are a tool that can be used to avert tragic outcomes: by restricting the number of herdsmen given access to the pasture, or the number of sheep that are allowed to graze, property helps avoiding over-depletion of resources.[231]

Follow-on scholarship—with a particular affinity for the economics of biomedical research—later identified the phenomenon of the anticommons.[232] In an anticommons, the (over)use of property rights contributes to the underuse of resources.[233] A tragedy happens when "multiple owners each have a right to exclude others from a scarce resource and no one has an effective privilege of use."[234]

The anticommons has also been described as fragmented ownership.[235] While the CMV vaccine case study does not embody a pure example of an anticommons—and rather a scenario involving non-cooperative firms for which transaction costs would otherwise be relatively small—it does illustrate the phenomenon of technology fragmentation. Individual firms have rights over three types of technology needed to produce a vaccine. Since, for the time being,[236] there are no cooperative efforts between these pharmaceutical companies, the progress of R&D on CMV is hampered by technology fragmentation.

Patents inherently restrict use.[237] That is precisely the mechanism that renders them valuable from an incentives perspective. In some cases, however, the mechanism that is deployed to incentivize vaccine races may induce siloed R&D that eventually brings the race to a halt altogether. The same legal regime designed to promote innovation—through the grant of proprietary rights—also works in ways that may constitute an explicit hurdle to collaborative forms of vaccine R&D. The following section argues that the specificities of vaccine R&D, alongside the public health benefits associated with vaccines, warrant the consideration of legal solutions tailored to this specific area of biopharmaceutical innovation.

B. THE NEED FOR ALTERNATIVE SOLUTIONS TAILORED TO VACCINE R&D

[230] *Id.*

[231] *Id.*

[232] See Michael S. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998). See also MICHAEL HELLER, THE GRIDLOCK ECONOMY, Basic Books (2008) (exploring the effects of anticommons in different areas).

[233] *Id.*, at 698.

[234] *Id.*, *ib*. See also Michael Heller, THE WEALTH OF THE COMMONS, http://wealthofthecommons.org/essay/tragedy-anticommons ("While private ownership usually increases wealth, too much ownership has the opposite effect: it wrecks markets, stops innovation, and costs lives.")

[235] See Ashish Arora and Robert P. Merges, *Property Rights, Firm Boundaries, and R&D Inputs*, unpublished manuscripts (2001), at 35.

[236] Interview with Dr. Plotkin, *supra* note 78 (noting that, through individual contacts at each one of the pharmaceutical companies involved in CMV R&D, it is possible that the situation might one day change).

[237] Heller & Eisenberg, at 699.

Theorists of innovation policy prescribe a mixed incentives approach to promote biopharmaceutical R&D.[238] Some of the proposed mechanisms include prizes,[239] grants[240] and R&D-related tax incentives.[241]

In the field of vaccines, strategies to ensure the maintenance of some levels of R&D have been in place for a while. The most commonly used is vaccine procurement by national governments[242] and international organizations,[243] which artificially builds demand for certain vaccines.[244] From the early 2000s onwards, the formation of partnerships bringing together the public and private sectors in an effort to bridge the valley of death in biopharmaceutical R&D became especially prominent.[245] Some of these partnerships operate specifically in the field of vaccines. The most representative examples are Gavi, which was established in 2000 to "improve access to new and underused vaccines" in the developing world,[246] and CEPI, established in 2017 to fund vaccine R&D for infectious diseases.[247]

Although these organizations are making impactful contributions to some areas of vaccine R&D,[248] their contributions primarily address the incentives side of patent related-inefficiencies.

---

[238] For a general discussion of available mechanisms to incentivize innovation beyond the sphere of patent law, see generally Benjamin N. Roin, *Intellectual Property Versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. 999 (2014); Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303 (2013); Steven Shavell & Tanguy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525 (2001).

[239] See generally James Love & Tim Hubbard, *Prizes for Innovation of New Medicines and Vaccines*, 18 ANN. HEALTH LAW 155 (2009).

[240] See generally W. Nicholson Price, *Grants*, BERKELEY TECH. L.J. (draft on file with author).

[241] Hemel & Ouellette, *supra* note 238.

[242] See generally Patrick Bajari & Steven Tadelis, *Incentives Versus Transaction Costs: A Theory of Procurement Contracts*, 32 RAND JOURNAL OF ECONOMICS 387 (2001). On the topic of vaccine procurement in the U.S., see Patricia M. Danzon, *Vaccine Supply: A Cross-National Perspective*, *supra* note 193, at 707 ("government purchasing tends to concentrate demand and reduce prices, depending on procurement strategies and the extent of competition").

[243] See E. Anthony Nelson et al., *Monitoring What Governments "Give for" and "Spend on" Vaccine Procurement: Vaccine Procurement Assistance and Vaccine Procurement Baseline*, 9 PLoS One e89593 (2014). See also Frederick M. Abbott, *Intellectual Property and Public Health: Meeting the Challenge of Sustainability*, Global Health Program Working Paper 7 (2011) (describing international procurement strategies for drugs and vaccines).

[244] Increasingly more complex models of procurement strategies have been proposed. See e.g. Nafiseh Shamsi et al., *An Option Contract for Vaccine Procurement Using the SIR Epidemic Model*, 267 EUR. J. OPERATIONAL RESEARCH 1122 (2018).

[245] See Jon F. Merz, INTELLECTUAL PROPERTY AND PRODUCT DEVELOPMENT PUBLIC/PRIVATE PARTNERSHIPS, FINAL REPORT TO THE WORLD HEALTH ORGANIZATION COMMISSION ON INTELLECTUAL PROPERTY RIGHTS, INNOVATION AND PUBLIC HEALTH (2005), at 17. See also Kent Buse & Amalia Waxman, *Public–private Health Partnerships: A Strategy for WHO*, 79 BULLETIN OF THE WORLD HEALTH ORG. 748, 748 (2001). (Tracing the history of public-private partnerships in the fields of drug R&D and drug procurement).

[246] GAVI, GAVI'S MISSION, https://www.gavi.org/about/mission/ (last accessed June 2019).

[247] COALITION FOR EPIDEMIC PREPAREDNESS INNOVATIONS [HEREINAFTER CEPI], CEPI MISSION, http://cepi.net/mission (last accessed June 2019).

[248] See e.g. Catherine Cheney, *CEPI, A Year In: How Can We Get Ready for the Next Pandemic?*, DEVEX (Feb. 5, 2018), https://www.devex.com/news/cepi-a-year-in-how-can-we-get-ready-for-the-next-pandemic-91987 (Describing CEPI's first funding projects) (last accessed June 2019); GAVI, VACCINE SUPPORT, https://www.gavi.org/support/nvs/ (Listing Gavi's ongoing work on 13 vaccines) (last accessed June 2019).

Similarly, mechanisms like prizes, grants or tax breaks can be deployed tin different ways to encourage investment in vaccine R&D, but they are not primarily designed to address transactional hurdles involving the development of new vaccines. While recognizing the need for mechanisms like public-private partnerships and a plurality of other innovation-enhancing tools, this Article takes a different route. It argues that the unique characteristics of vaccine R&D and vaccine markets require novel solutions in the form of tailored legal interventions to establish partly differentiated legal regimes governing vaccine innovation, as detailed in the following sections.

As a principle, there are reasons not to endorse technology-specific reforms, especially those resulting in the adoption of overly specialized legal regimes.[249] Scholars have cautioned against the perils of abandoning uniformity in favor of industry-specific rules, particularly in the context of incentives theory and intellectual property.[250] Concerns with industry capture and rent-seeking behavior drive one line of criticism.[251] Congress has on multiple occasions enacted statutes tailored to the needs articulated by specific industries,[252] and has been especially responsive to the pharmaceutical industry.[253] Moreover, it is unclear whether the adoption of industry-specific statutes would "respond to changing circumstances" any better than existing uniform legal regimes.[254] Crafting a separate set of rules applicable to particular industries also artificially delineates the boundaries of technology, potentially leadings to contradictory outcomes in the case of boundary-spanning technologies.[255] Finally, a move towards specialized legal regimes applicable to particular forms of technology would entail high administrative costs and impose steep learning curves on the judiciary,[256] not to mention a massive legislative overhaul of long-established regimes.

This Article agrees with all of these propositions. It does not suggest that vaccine innovation—from incentives embedded in the current patent regime to provisions governing technology transfer—should be the subject of separate legislative treatment. It does not advocate for a comprehensive ad hoc regime regulating all aspects of vaccine development and transfer of vaccine technology.[257] Rather, it proposes individual measures, most of them requiring a certain degree of legislative intervention, that reflect the specific conditions surrounding vaccine R&D without changing the entire legal regime governing biotechnologies, or technical and scientific innovation in general.

---

[249] See generally Mark A. Lemley & Dan L. Burk, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575 (2003) (cautioning against technology-specific legislative approaches in patent law).

[250] See Michael W. Carroll, *One Size Does Not Fit All: A Framework for Tailoring Intellectual Property Rights*, 70 OHIO ST. L. J. 1361, 1365 (2009) (describing narratives of patent law as a unitary field). Cfr. Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)*, Nat'l Bureau of Econ. Res., Working Paper No. 7552 (2000) (comparing differentiated use of the patent system by different types of industries).

[251] Lemley & Dan L. Burk, *Policy Levers*, at 1578.

[252] *Id.*, at 1631 (listing statutes that were the product of Congressional action in response to requests of specific industries).

[253] *Id., ib.* See also John Abraham, *The Pharmaceutical Industry as a Political Player*, 360 LANCET 1498 (2002).

[254] Lemley & Dan L. Burk, *Policy Levers*, at 1578; see also *id.*, at 1634.

[255] *Id.*, at 1636.

[256] *Id.*, at 1635-1637.

[257] Much less vaccine administration.

Discussions on the drawbacks of industry-specific regimes take place at a panoramic level: they consider the category of biotechnology as a whole as opposed to software, for instance, not specific biotechnologies.[258] Advocating for an ad hoc regime—even if only an ad hoc patent regime—for different types of biotechnologies would run into the same types of problems outlined above with respect to broader categories and corresponding industries. But recognizing that a specific area of biotechnology would benefit from tailored legislative or policy interventions is a different proposition. The following section explores how one such intervention could take place, cognizant of the political economy wherever possible.

C. Proposed Framework for Narrowly Construed "Take-and-Pay" Regimes

This proposal focuses on the transactional side of vaccine innovation, defined as transfers of vaccine technology needed for follow-on or complementary R&D in the field of vaccines. It considers the adoption of "take-and-pay" regimes applicable to vaccine-related technologies covered by proprietary rights.

"Take-and-pay" regimes are often referred to as liability regimes, in a different sense from the one used in discussions about tort-based liability arising from problems related to the administration of a vaccine.[259] In the context discussed here, liability rules are distinguishable from property rules, as per the Calabresi-Melamed formulation.[260] In general terms, a liability rule gives a person the ability to pay an "objectively determined value" for someone else's entitlement.[261] In this sense, liability rules are a way of overcoming the transaction costs associated with determining the cost of the entitlement.[262]

The default legal regime to promote innovation grants inventors property-like rights that cover a meritorious technical achievement.[263] If someone else wishes to use technology covered by proprietary rights, the patent holder has to agree to that use, as well as to the conditions under

---

[258] For the question of how different technologies have fared under the uniform regime of patent law, see generally Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 Berkeley Tech. L.J. 1155 (2002).

[259] See *supra* note 79 and accompanying text.

[260] See Guido Calabresi & A. Douglas Melamed, *Property Rules, Liability Rules, and Inalienability: One View of the Cathedral*, 85 Harv. L. Rev. 1089, 1092 (1972) (defining liability regimes as situations in which "someone may destroy the initial entitlement if he is willing to pay an objectively determined value for it").

[261] *Id.*, at 1092. Some scholars have framed liability rules in terms of options ("A liability rule gives at least one party an option to take an entitlement nonconsensually and pay the entitlement owner some exercise price"); see Jack M. Balkin & Ian Ayres, *Entitlements as Auctions: Property Rules, Liability Rules, and Beyond*, 106 XX 703, 704 (summarizing the literature on entitlements as options). Balkin and Ayres have also proposed construing liability rules as auctions ("Viewing entitlements as auctions implies that after one party exercises its option to take nonconsensually, the other has an option to 'take back,' and so on, for some number of rounds."). *Id.*, at 707.

[262] Calabresi & Melamed, at 1106, 1110.

[263] There is an ongoing debate among scholars on the topic of whether patents should be considered property rights or administrative entitlements. See e.g. Jonathan M. Barnett, *The Patent System at a Crossroads*, 41 Regulation 44 (2018). The Supreme Court has recently weighed in on an aspect of this debate, applying the public-rights doctrine to uphold the validity of administrative procedures that may result in the invalidation of patent rights; the ruling seems to support the idea that patents cannot be considered property qua tale. See *Oil States Energy Services, LLC v. Greene's Energy Group*, LLC, 584 U.S. _ (2018). Nevertheless, for purposes of the present analysis, it is sufficient to establish that patents confer a right to exclude others. See U.S. Const. art. I, § 8, cl. 8 (granting Congress the power "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries").

which such use may occur. Recall the case of the CMV vaccine:[264] three components needed to develop a working vaccine candidate are scattered among different firms. Since, for the time being, these firms are not cooperating, any patented technology needed for vaccine R&D has to be licensed, or ownership of the technology has to be transferred from the rights holder(s). In this sense, our innovation system is predicated on an approach that has traits of a property regime.[265]

By contrast, a liability regime would treat this situation differently. Under a liability rule, someone interested in using the technology for R&D purposes could "take" it in exchange for "payment" for the patentee's entitlement. The rights holder would not be able to oppose the use of the technology—something that cuts against the customary workings of intellectual property law—but in return he or she would be compensated for that use. Conversely, the person or company using the technology would not be required to engage in negotiations with the rights holder (and support other transaction costs) and would swiftly gain access to the technology upon payment of an "objectively determined value."[266]

The choice to protect entitlements through liability rules is most commonly justified by principles of economic efficiency,[267] distributive goals[268] or other social justice goals,[269] including the promotion of socially desirable innovation.[270] Because the current legal regime incentivizing innovation is incapable of generating appropriate levels of R&D in the field of vaccines, and because of the especially difficult circumstances that surround vaccine R&D, a liability regime designed solely to cover transfers of vaccine-related technology for R&D purposes[271] would be in line with these principles. It would promote economic efficiency by lowering transaction costs associated with bargaining. And it would pursue social justice goals by facilitating the development of a technology that, as seen in Parts I and II, is widely accepted as welfare-enhancing.[272]

Jerome Reichman has proposed the adoption of liability regimes at a much broader level, in situations in which property or property-like regimes are inefficient or socially undesirable, hindering innovation.[273] Liability rules would be used much more extensively, creating a "general purpose innovation law," a system fueled by "off-the-rack liability rules" that follow-on innovators could use as needed.[274] The proposal stems from an overarching analysis of how intellectual

---

[264] *Supra*, Part III.A.

[265] Calabresi & Melamed, at 1092 ("An entitlement is protected by a property rule to the extent that someone who wishes to remove the entitlement from its holder must buy it from him in a voluntary transaction in which the value of the entitlement is agreed upon by the seller").

[266] *Id., ib.*

[267] *Id.*, at 1093.

[268] *Id.*, at 1098. Calabresi and Melamed note that "distributional goals are expensive and difficult to achieve, and the collective valuation involved in liability rules readily lends itself to promoting distributional goals." *Id.*, at 1110.

[269] *Id.*, at 1106.

[270] See Jerome H. Reichman, *Legal Hybrids Between the Patent and Copyright Paradigms*, 94 COLUM. L. REV. 2432, 2445 (1995).

[271] And not for stand-alone commercialization of the patent-protected technology.

[272] See e.g. *supra* note 160.

[273] See generally Reichman, *Legal Hybrids*, *supra* note 270.

[274] *Id.*, at 2533.

property, in the many shapes it currently takes, may slow down or deter innovation across the technology spectrum.[275]

The liability approach proposed in this Article is of much more limited scope, applying only to vaccines given the extraordinary challenges faced by vaccine-related R&D. Because it is technology-specific, this proposal is also less likely to affect the expectations and vested interests of the industry potentially affected by a shift to a liability regime.

Authors like Robert Merges have explored the possibility of industry self-regulation by "contracting into liability rules."[276] One of the ideas behind self-regulation is that the goal of lowering transaction costs can best be achieved through self-organizing private institutions, which are motivated to enter the field and possess greater expertise in the subject matter.[277] Examples of industry self-regulation include the creation of collection societies like ASCAP and BMI in the field of copyright, or technology "pools" in patents.[278] Patent pools are contractual arrangements that enable rights holders to share patented technology by "commit[ing] their patents to a single holder, who then licenses them out to the original patentees and perhaps to outsiders."[279] An example of a patent pool in the biopharmaceutical sphere is the Medicines Patent Pool, which is backed by the United Nations and pools technology for developing countries, with a focus on HIV, hepatitis C and tuberculosis.[280] The World Health Organization supports the view that patent pools are a valuable policy tool to promote innovation.[281] The problem with patent pools in biotechnology is that they are seldom used.[282] Unlike most of the examples surveyed in literature on industry self-regulation, biotechnology industries do not successfully resort to pooling.[283]

Against this backdrop, and even though the mechanism proposed in this Article is a liability regime for a relatively small industry, the probability that the industry would self-regulate is low, as illustrated by the case of the CMV vaccine. Rather than waiting for self-regulation to occur, the approach that would best further the goal of promoting socially valuable innovation would be a legislative intervention.

Proposals that entail legislative action are always confronted with the challenges of the political economy, which is especially fraught with competing interests in the field of biopharmaceutical innovation. However, unlike most other areas in biotechnology, vaccine R&D

---

[275] The Author discusses the proliferation of hybrid legal regimes that regulate innovation but do not fall under the classic patent-copyright dichotomy, and develops his proposal in connection with trade secrecy. See e.g. *id.*, at 2436-37.

[276] See Robert P. Merges, *Contracting into Liability Rules: Intellectual Property Rights and Collective Rights Organizations*, 84 CAL. L. REV. 1293 (1996).

[277] *Id.* The mechanisms of self-regulation have been explored in a broad range of contexts outside the field of R&D and technical innovation. See e.g. ELINOR OSTROM, GOVERNING THE COMMONS: THE EVOLUTION OF INSTITUTIONS FOR COLLECTIVE ACTION, Cambridge University Press (1990).

[278] Merges, *Contracting into Liability Rules*, at 1295.

[279] See Erik Hovenkamp & Herbert Hovenkamp, *Patent Pools and Related Technology Sharing*, in CAMBRIDGE HANDBOOK OF ANTITRUST, INTELLECTUAL PROPERTY, AND HIGH TECH (ROGER D. BLAIR & D. DANIEL SOKOL, EDS.) Cambridge University Press (2017).

[280] MEDICINES PATENT POOL, https://medicinespatentpool.org.

[281] WORLD HEALTH ORG., GLOBAL STRATEGY AND PLAN OF ACTION ON PUBLIC HEALTH, INNOVATION AND INTELLECTUAL PROPERTY (2008). See also Ryan Lampe & Petra Moser, *Patent Pools, Competition, and Innovation—Evidence from 20 US Industries under the New Deal*, 34 J. LAW, ECON. & ORG. 1, 1 (2016).

[282] Merges, *Contracting into Liability Rules*, at 1355 (attributing part of the cause for this to antitrust regulation).

[283] *Id.* (examining the aircraft manufacturing, bed and automobile industries).

is *expected* to be unprofitable. Consider, for instance, the stance on vaccine profitability of the most important public-private partnerships supporting vaccine R&D, CEPI.[284] CEPI's business model is entirely designed around the idea that the successful development of CEPI-funded vaccines is likely to never turn a profit.[285] In fact, the organization business plan explicitly states that "[it is anticipated that vaccines developed with CEPI support will not be profitable."[286]

Given the specificities of vaccine development within the larger dynamics under which the pharmaceutical industry typically operates, and in particular the relative size of vaccine markets, the proposal advanced in this Article disturbs the status quo as minimally as possible.

It is also possible to further narrow the scope of a vaccine-centric liability regime. For instance, it is possible to exclude cutting-edge vaccine technologies like the ones currently used in the development of DNA vaccines.[287] Doing so would maintain the traditional framework for R&D in areas where science is still in early or exploratory stages, while bringing established (and consequently less valuable) technology into the "take-and-pay" model. For instance, the liability regime could be restricted to sub-sets of vaccine technology, or be made to be disease-specific (including infectious diseases and excluding, for example, cancer vaccines).[288] It is also possible to have a discrete list of types of vaccines that are subject to a liability regime, much in the same way that there are already lists of eligible diseases for incentives like the U.S. Food and Drug Administration priority review vouchers currently awarded to sponsors of approved drugs in a limited range of areas.[289]

A reasonable objection to a narrowly construed liability regime as the one proposed here is that it might produce minimal or second-rate innovation, as more recent vaccine technology remains under a property-like regime. While this is true, consider that such an approach would nonetheless enable access to most of the technology used today to manufacture most of the vaccines administered across the globe.[290]

A final problem with crafting a liability regime is the difficulty in determining the appropriate price for the entitlement. Proponents of liability regimes in other contexts have suggested that this can be resolved by the establishment of a "fixed price menu."[291] Such a solution would be particularly manageable in the context of a liability regime circumscribed to vaccines. Instead of a fixed list of prices, the menu could take the shape of a relatively simple formula, which would allow the parties to take into account different variables, and which could be updated and

---

[284] See *supra* note 247 and accompanying text.

[285] CEPI, PRELIMINARY BUSINESS PLAN, 2017-2021 (November 2016) (hereinafter PRELIMINARY BUSINESS PLAN) (on file with author), at 12.

[286] *Id., ib.*

[287] See *supra*, note 4 and accompanying text.

[288] *Id*.

[289] David B. Ridley et al., *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313, 313 (2006) (first proposing the voucher regime). See also Andrew Witty, *New Strategies for Innovation in Global Health: A Pharmaceutical Industry Perspective*, 30 HEALTH AFF. 118, 124 (2011).

[290] See *supra*, note 4 and accompanying text

[291] *Id.*, at 1377. On a related note, problems of under-compensation that are often associated with liability regimes would be less salient in this context, as most vaccine manufacturers are not expecting economic returns on their investment. See Michael Mattioli, *Power and Governance In Patent Pools*, 27 HARV. J.L. & TECH. 421, 434 (2014) (noting that "[e]mpirical evidence supports the argument that inventors would be under-compensated in a compulsory licensing regime").

added to in order to reflect changes in technological development, market evaluations or general economic climate.

CONCLUSION

The development of new vaccines has long been understood as a public health priority, particularly in the field of infectious diseases. Vaccine R&D, however, is adversely affected by funding and transactional problems. This Article has explored the reasons behind this misalignment, with a focus on the role of intellectual property at the tail end of vaccine races.

While certain legal and policy interventions have historically been used to incentivize vaccine R&D, they leave unanswered questions related to vaccine technology transfer, such as the lack of collaborative R&D efforts in contexts of technology fragmentation. Given the particular characteristics of vaccine R&D, the Article has argued in favor of technology-specific legal interventions designed to facilitate innovation in this idiosyncratic field. The specific intervention proposed here takes the form of a legislatively construed "take-and-pay" regime. This regime would create a pathway for follow-on innovators to access and use vaccine technology covered by proprietary rights, and hence overcome the problem of technology dispersion.

At a broader level, the Article has sought to advance the scholarly and policy debates on normative approaches to the promotion and diffusion of innovation in different fields of biotechnology. As emerging biotechnologies keep challenging the boundaries of existing regimes designed to promote innovation, it is crucial that we keep refining our legal tools and analytical frameworks to ensure the development and availability of socially desirable technologies.