

4-9-2013

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Vincent Y. Ling J.D., M.S.

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Recommended Citation

Ling, Vincent Y. J.D., M.S. (2013) "Emerging Partially Effective Vaccines: Ethical and Policy Considerations," *North Carolina Central University Science & Intellectual Property Law Review*: Vol. 6 : Iss. 1 , Article 2.
Available at: <https://archives.law.nccu.edu/siplr/vol6/iss1/2>

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EMERGING PARTIALLY EFFECTIVE VACCINES: ETHICAL AND POLICY CONSIDERATIONS

*Vincent Y. Ling**

Abstract

An efficacy showing is one prerequisite for the market approval of vaccines in the United States. The Food and Drug Administration's current standard for efficacy is relatively vague and does not require comparative effectiveness data or impose strict post-marketing regulation. Meanwhile, there is an urgent medical need for many emerging vaccines that are partially effective, including therapeutic vaccines for diseases such as malaria and cancer. The framework for vaccine efficacy needs to be updated to address this changing vaccine landscape while balancing the need for emerging vaccines to enter the market. This Article considers the ethical implications of partially effective vaccines and proposes policy and regulatory reforms for an efficacy framework that emphasizes comparative effectiveness research, mandates post-approval clinical trials and tracks the long-term effectiveness of vaccines without hindering the entrance of urgently needed vaccines.

Introduction

An efficacy showing is a prerequisite for the market approval of vaccines in the United States, but vaccines are never 100% effective for a variety of reasons. Vaccines may not confer their intended benefits to partial- or non-responders, and many are strain-specific. Furthermore, vaccines often grant immunity for only a limited period of time, so efficacy can vary based on administration schedules or follow-up booster vaccines.

The United States Food and Drug Administration ("FDA") currently imposes an efficacy requirement for vaccine approval that has not been substantially updated since 1972. The standards for the quality and quantity of supporting efficacy data are outdated and relatively vague. As partially effective vaccines become more prevalent on the market, we must confront the ethical issues that these vaccines pose and reconsider the current framework for efficacy.

* J.D. and Master of Bioethics, University of Pennsylvania. I would like to thank Dr. Arthur Caplan for his support and guidance on this Article.

Part I begins by providing background on partially effective vaccines and the weaknesses of the current efficacy standard. Part II then confronts the ethical dilemma of using partially effective vaccines. It also gives special consideration to an emerging class of partially effective vaccines—therapeutic vaccines. Finally, Part III discusses the policy and regulatory reform that may be necessary to update the current efficacy standard.

I. Background on Partially Effective Vaccines

A. Defining “Partially Effective Vaccine”

As a threshold matter, no vaccine is 100% effective.¹ Vaccines may be considered partially effective in many ways—for example, for being strain-specific, short-lived or less effective if not administered in multiple doses or according to an appropriate timetable.² Moreover, vaccine efficacy³ can vary in individuals due to factors such as ethnicity, age or genetic predisposition.⁴ Some individuals, known as partial- or non-responders, have immune systems that fail to respond adequately or at all to certain vaccines.⁵ The term “par-

1. See Thomas May, *Public Communication, Risk Perception, and the Viability of Preventive Vaccination Against Communicable Diseases*, 19 *BIOETHICS* 407, 412-13 (2005) (describing how vaccination of a critical mass of a population can result in herd immunity, despite no vaccine being 100% effective.).

2. See U.S. DEP’T OF HEALTH & HUMAN SERVS., *GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS* 8–9 (May 1998), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ucm078749.pdf>.

3. “Efficacy” and “effectiveness,” as the terms are conventionally used, are distinct. Efficacy of a vaccine is demonstrated in controlled clinical trials, while effectiveness is observed in the context of the real world, on a diverse population with indirect effects and compounding factors, like other illnesses. See M. Elizabeth Halloran et al., *Direct and Indirect Effects in Vaccine Efficacy and Effectiveness*, 133 *AM. J. EPIDEMIOLOGY* 323, 323-24 (1991) (“The term ‘efficacy’ has been applied to estimates of efficacy parameters obtained from controlled prospective trials, while ‘effectiveness’ has been used for estimates of efficacy obtained from observational studies.”); Heath Kelly & Marta Valenciano, Comment, *Estimating the Effect of Influenza Vaccines*, *LANCET ONLINE* 1, 1 (Oct. 26, 2011) (defining “efficacy” and “effectiveness” similarly).

4. See U.S. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 2, at 2.

5. See *id.* at 7–9.

tially effective vaccine” can thus be used in different contexts, and there are generally two ways of defining it.⁶

The first, and more easily understood, definition of “partially effective vaccine” is a vaccine “that protects some people in a population, but not others.”⁷ This definition is useful in the context of anti-infection and anti-transmission vaccines such as prophylactic vaccines, or immunizations, that provide protection against infection in the first place.⁸ These vaccines are unique from other medical treatments in that they implicate benefits to third parties, not just the individual receiving the vaccination.⁹ The objective of using prophylactic vaccines is often to attain a health benefit to a community or population—a concept called herd immunity.¹⁰ Herd immunity can result when a critical mass of a population is immunized, even if the vaccine is not 100% effective for individuals.¹¹ Except when discussing therapeutic vaccines, this Article uses “partially effective vaccines” in accordance with this first definition.

The second definition for “partially effective vaccine” is “a vaccine which [does not] completely prevent infection by a pathogen but helps reduce the severity of the disease it causes.”¹² This second definition is useful when discussing anti-toxin and anti-growth vaccines, which do not prevent disease or infection but improve an individual’s ability to fight disease or infection. This definition will be relevant to the discussion of therapeutic vaccines.

6. Emily Bass, *Partially Effective Vaccines*, in AIDS VACCINE HANDBOOK 59, 59–60 (Patricia Kahn ed., 2d ed. 2005), available at <http://www.avac.org/ht/a/GetDocumentAction/i/2634>.

7. *Id.* at 60.

8. *Id.*

9. See TOM L. BEAUCHAMP & JAMES F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS 168 (5th ed. 2001) (noting that vaccinations provide “a major benefit to other parts of the population” beyond the individual).

10. See Robert I. Field & Arthur L. Caplan, *Evidence-Based Decision Making for Vaccines: The Need for an Ethical Foundation*, 30 VACCINE 1009, 1009-13 (2012); see also May, *supra* note 1, at 412-13 (“If a critical mass of people is immune [because of receiving vaccines], then, those who are not immune are protected.”).

11. See May, *supra* note 1, at 412-13.

12. Bass, *supra* note 6, at 60.

B. The Efficacy Standard for FDA Approval: “Adequate and Well-Controlled Studies”

The process of getting vaccines to the market in the United States is a time-consuming endeavor, sometimes taking up to ten years. A vaccine manufacturer must obtain licenses for the biological product itself and the manufacturing establishment by filing two applications with the FDA—an Investigational New Drug Application (“IND”) and a Biologics License Application.¹³ It is during the IND process that a manufacturer must demonstrate efficacy, in addition to showings of safety, immunogenicity, and proper dosage ranges.¹⁴

The FDA’s first requirement for a demonstration of vaccine efficacy was adopted in the mid-twentieth century.¹⁵ In 1944, the Public Health Service Act (“the Act”) implemented regulations for government licensing of biological products, including vaccines.¹⁶ Under § 262 of the Act, vaccines must demonstrate “continued safety, purity, and potency,” of which “‘potency’ has long been interpreted to include effectiveness.”¹⁷ The precise efficacy showing required by the statute, however, was anyone’s guess and sparked much debate.¹⁸ Subsequently, the FDA conducted a review of existing product safety and efficacy in 1972 and concluded that the standard for proving vaccine efficacy requires “adequate and well-controlled studies”—the same standard that non-biologic drugs seeking FDA approval under the Federal Food, Drug, and Cosmetic Act (“FDC Act”) must meet.¹⁹ This standard encompasses three aspects of necessary evidence: type, quality, and quantity.²⁰

13. See 21 U.S.C. §§ 355(a), (b) (2006); 42 U.S.C. §§ 262(a), (k) (2006).

14. Rosemary Tiernan, Ctr. for Biologics Evaluation & Research, Presentation to the Nat’l Inst. of Allergy and Infectious Diseases, Regulatory Perspective on Development of Preventative Vaccines for Global Infectious Diseases 9 (Oct. 30, 2007), [http://www.//s///. .](http://www.//s///.)

15. Public Health Service Act, ch. 373, 58 Stat. 702 (1944) (codified as amended at 42 U.S.C. § 262 (2006)).

16. 42 U.S.C. §§ 201–300 (2006).

17. See U.S. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 2, at 4 (citing 21 C.F.R. § 600.3(s) (2010)).

18. See *id.* at 1 (“[T]he issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others.”).

19. Adequate and Well-Controlled Studies, 21 C.F.R. § 314.126 (2012).

20. *Id.*

1. The Type of Evidence Required to Show Efficacy

Under the “adequate and well-controlled studies” standard, trials to demonstrate efficacy must be designed to “meet local and international ethics standards [and be deemed] good clinical practices.”²¹ Typically, manufacturers demonstrate vaccine efficacy by conducting controlled studies on human volunteers and observing clinical endpoints (measurable objective results) like infection rate.²² Efforts should also be made “to identify immune correlates of protection,” and in some cases, approval may be based solely on such assessments of immunogenicity.²³ Clinical trials usually occur in three or more incremental phases: Phase I involves twenty to one hundred human subjects over several months and is conducted to demonstrate basic safety and to identify severe adverse events; Phase II expands the trial to several hundred subjects over a time frame of up to two years to further evaluate safety and efficacy; and Phase III continues studying safety and efficacy over an even longer period and may include up to several thousand volunteers.²⁴ If, at any time, results demonstrate safety concerns or lack of efficacy, the study may be halted, and subsequent phases will not be reached.²⁵

In some cases, human studies may be impractical or unethical. To address this issue, “the FDA instituted a regulatory exception [in 2002] permitting the licensure of certain vaccines . . . without data from human efficacy studies.”²⁶ This exception permits licensure as long as the pathophysiological mechanism of a vaccine is well understood, the efficacy is demonstrated in more than one animal species that is predictive of human response and the animal endpoint is clearly related to a human endpoint.²⁷ In the national security con-

21. Tiernan, *supra* note 14, at 6. For standards of good clinical practice (“GCP”), see U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: E6 GOOD CLINICAL PRACTICE: CONSOLIDATED GUIDANCE (Apr. 1996), <http://www.fda.gov/downloads/III/Guidances/ucm073122.pdf>.

22. Tiernan, *supra* note 14, at 12.

23. Lydia A. Falk & Leslie K. Ball, *Current Status and Future Trends in Vaccine Regulation—USA*, 19 VACCINE 1567, 1569–70 (2001).

24. Isadora Stehlin, *How the FDA Works to Ensure Vaccine Safety*, FDA CONSUMER MAGAZINE 2 (Dec. 1995), available at <http://www.anthrax.osd.mil/documents/library/HowFDAWorks.pdf>.

25. *Id.*

26. See Katelin Hoskins, *Vaccines and Bioterrorism: Obstacles to Bioterror Vaccine Development*, VACCINE ETHICS.ORG (July 2010), http://www.vaccineethics.org/issue/_development.php; see also Tiernan, *supra* note 14, at 11.

27. *Id.*

text, this rule allows for the use of animal studies as substantial evidence of efficacy for vaccines that protect against “lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances.”²⁸

2. The Quantity of Evidence Required to Show Efficacy

Traditionally, “the FDA requires [vaccine] manufacturers to submit at least two ‘adequate and well-controlled’ studies” demonstrating efficacy.²⁹ The FDA bases its rationale for the two-study requirement on the language in § 505(d) of the FDC Act, which “uses the plural form in defining ‘substantial evidence’ as ‘adequate and well-controlled *investigations*, including clinical *investigations*.’”³⁰

Nevertheless, in some instances, the FDA has approved new vaccines in reliance on just one especially compelling or persuasive study.³¹ The FDA is more likely to rely on a single study if the efficacy data is supported by related studies that investigate different doses, regimens, or endpoints.³²

3. The Quality of Evidence Required to Show Efficacy

Finally, parties seeking to obtain FDA approval of vaccines must submit documentation showing that the efficacy studies were properly designed and conducted.³³ Requirements regarding the quality of the studies include “extensive documentation of trial planning, protocols, conduct, and data handling,” as well as patient records.³⁴

While the extent of required documentation varies on a case-by-case basis, the quality of evidence, for purposes of meeting the “ade-

28. FDA Biologics Licensing Rule, 21 C.F.R. § 601.91 (2010); *see also* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GENERAL PRINCIPLES FOR THE DEVELOPMENT OF VACCINES TO PROTECT AGAINST GLOBAL INFECTIOUS DISEASES (Dec. 2011), <http://www.fda.gov/oc/Guidances/Vaccines/>.pdf.

29. *See, e.g.*, Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3d Cir. 1986); *see also* U.S. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 2, at 3.

30. *See* U.S. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 2, at 3, n.4 (emphasis added); *see also* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 505 (2006).

31. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 2, at 3.

32. *Id.*

33. *Id.* at 16.

34. *Id.*; *see also* Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.126 (2010).

quate and well-controlled” standard, usually refers to: “(1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records . . . for the purposes of verifying the data.”³⁵ If the FDA does not have full access to clinical data or detailed study reports, it may nonetheless rely on the efficacy findings in considerationlight of other factors, such as independent published literature that enhances the data.³⁶

C. The Current Regulatory Standard for Vaccine Efficacy

1. No Bright Line Efficacy Threshold

In light of the foregoing guidelines, the FDA’s efficacy standard is relatively vague and determined on a case-by-case basis. It has no bright line rule for what evidence constitutes proof of vaccine efficacy. Instead, the agency takes a more fluid approach by looking at the quantity and quality, as well as the type, of evidence submitted.³⁷ For example, all other factors equal, large, multicenter studies and rigorous studies with accessible data are more persuasive than smaller or incompletely documented studies.³⁸ The guidance, however, stops there.

In some cases, the FDA has approved prophylactic vaccines based on a single adequate and well-controlled trial showing an 80% efficacy rate at a 95% confidence interval.³⁹ The agency considers such an efficacy percentage to be “statistically very persuasive.”⁴⁰ There are many vaccines on the U.S. market, however, with overall efficacy rates lower than 80%. For instance, the original polio vaccine is only about 60% effective,⁴¹ and studies have estimated the efficacy of licensed influenza vaccines to be between 59%-73% in adults.⁴²

35. See U.S. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 2, at 16.

36. See *id.* at 17-19 (noting that the FDA has approved drugs and biologics based solely on published reports).

37. See *id.* at 2-20 (providing guidance regarding the quantity and quality of evidence necessary to support vaccine efficacy).

38. See *id.* at 12.

39. See *id.* at 15.

40. *Id.*

41. See Bass, *supra* note 6, at 60.

42. Kelly & Valenciano, *supra* note 3, at 1 (summarizing reported meta-analyses on the efficacy of influenza vaccines licensed in the United States).

There has been criticism that the FDA's standards for vaccine approval are not stringent enough.⁴³ As Avorn notes, however, the issue with the efficacy standard "resides not in the quality of execution the FDA requires . . . but in the questions it asks."⁴⁴ Although the FDA's current efficacy standard does not require any threshold efficacy, such a flexible standard is reasonable in light of the various types of vaccines and the public's need for them. More problematic is the standard's lack of any comparative effectiveness requirement—the FDA does not specifically inquire into whether a vaccine is *more* effective than other vaccines or treatments, or whether it is less effective in certain subpopulations.⁴⁵

2. Showing Vaccine Efficacy in Practice

In practice, vaccine trials are usually larger than drug trials. For instance, the efficacy of the quadrivalent human papillomavirus ("HPV") vaccine, Gardasil, was studied in over 17,000 women in Phase III trials.⁴⁶ The bivalent HPV vaccine, Cervarix, was approved based on two Phase III efficacy trials involving over 19,000 participants.⁴⁷ By comparison, efficacy trials for drugs, even blockbuster drugs, generally involve a few dozen to a few hundred participants (though studies for comparative effectiveness or effectiveness in targeted subpopulations occasionally recruit over a thousand participants).⁴⁸

43. See, e.g., Jerry Avorn, *FDA Standards—Good Enough for Government Work?*, 353 NEW ENG. J. MED. 969, 969–72 (2005); Alastair J.J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618, 618–23 (2006).

44. Avorn, *supra* note 43, at 969.

45. *Id.* at 969-70.

46. Lauri E. Markowitz et al., Ctrs. for Disease Control & Prevention, *Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices*, 56 MORBIDITY & MORTALITY WKLY. REP., RR-2, Mar. 23, 2007, available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr56e312a1.htm>.

47. U.S. Food & Drug Admin., *FDA Approves New Vaccine for Prevention of Cervical Cancer*, FDA.GOV (Oct. 16, 2009), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm187048.htm>; GlaxoSmithKline, *Package Insert & Patient Information - Cervarix*, §§ 13–16, available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf>.

48. CLINICALTRIALS.GOV, <http://clinicaltrials.gov/ct2/home> (last visited Feb. 22, 2012) (searching for the number of participants in Phase III efficacy trials for

The larger vaccine trials are likely driven more by clinical necessity than by regulatory requirement.⁴⁹ While clinical drug trials typically study benefits to patients who already exhibit a targeted indication, prophylactic vaccine trials aim to demonstrate a protection against infection or disease in an inoculated group compared to an uninoculated group.⁵⁰ Traditionally, prophylactic vaccines target the general population rather than subpopulations with specific indications, so the vast majority of participants in a clinical trial for a prophylactic vaccine will never develop the targeted condition, with or without vaccination.⁵¹ All else equal, the lower the rate of incidence and the lower the target efficacy, the larger the sample size required to obtain statistically significant trial results.⁵²

Therefore, the standard for vaccine efficacy evidence in practice may be driven in part by statistical necessity, in addition to the FDA's regulatory standards. But even so, the current regulatory standard may not be sufficiently tailored for the emerging vaccine market. New vaccines targeting more complex indications, like Human Immunodeficiency Virus ("HIV") and cancer, may have lower-than-

blockbuster drugs like esomeprazole [Nexium], omeprazole [Prilosec], and atorvastation calcium [Lipitor]).

49. Larger vaccine trials are also probably not the result of concerns about legal liability because the National Vaccine Injury Compensation Program provides predetermined, capped compensation from a trust fund for certain vaccine-related injuries and deaths. See National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-1 to -34 (2006); see also *History of Vaccine Safety*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/vaccinesafety/vaccine_monitoring/history.html (last visited Oct. 26, 2012) (offering the motivation behind Congress's establishment of the National Vaccine Injury Compensation Program).

50. *Compare Introduction, Trial Phases, Trial Design*, GENENTECH, <http://www.biooncology.com/clinical-trials/clinical-endpoints/introduction/index.html> (last accessed Nov. 1, 2012) (describing general clinical trial design to include the selection of a patient population that *already* exhibits disease state and will likely benefit from the intervention being tested (emphasis added)), with Halloran et al., *supra* note 3, at 323-24 (noting that the interest in a vaccine is in its protection *against* infection or disease, and requiring, in valid efficacy and effectiveness studies, that "exposure to the disease . . . be identical in the case of . . . inoculated and uninoculated persons" (emphasis added)).

51. Dennis O. Dixon et al., *HIV Vaccine Trials: Some Design Issues Including Sample Size Calculation*, 6 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 485, 492 (1993) (explaining that, to obtain statistically significant results in vaccine trials, large sample sizes are required because of low rates of infection).

52. See *id.*; R.T. O'Neill, *On Sample Sizes to Estimate the Protective Efficacy of a Vaccine*, 7 STAT. MED. 1279 (1988).

typical efficacy rates. Furthermore, the efficacy standard may not be enough to encourage continued development of more effective vaccines.

II. The Ethics of Partially Effective Vaccines

Ethically, the least problematic use of partially effective vaccines would be where there are no alternative vaccines available. For example, in certain emergency situations implicating national security, there may be no other practical interventions. The importance of partially effective vaccines in such scenarios is reflected by the FDA's policy of allowing animal studies to show the efficacy of vaccines against "lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances."⁵³ Congress also recognized this need after 9/11 by passing the Project BioShield Act of 2004 ("BioShield Act"), which provided \$5 billion in funding for buying vaccines to protect against bioterrorist attacks.⁵⁴ The BioShield Act established the Emergency Use Authorization ("EUA") program to allow the FDA "to approve the emergency use of drugs, devices, and medical products . . . that were not previously approved, cleared, or licensed by FDA . . . in certain well-defined emergency situations."⁵⁵ Thus, in certain emergency public health scenarios, partially effective vaccines may be an imperfect, but necessary, solution.

Thornier ethical issues arise if there are more effective vaccines available or if the development of more effective vaccines is imminent. An overarching question may be posed: is it ethical to provide partially effective vaccines to populations that desperately need them, even if there are, or may be, more effective vaccines? This Part examines the ethical question under utilitarian and deontological

53. 21 C.F.R. § 601.90 (2012); see U.S. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 2, at 4.

54. Project BioShield Act of 2004, Pub. L. No. 108-276, § 3, 118 Stat. 835, 852 (2004).

55. Specifically, for a vaccine to receive accelerated approval under the EUA, three steps must first be taken: (1) the Secretary of Homeland Security, Secretary of Defense, or Secretary of HHS must determine an emergency justifying issuance of an EUA; (2) the Secretary of HHS must declare the emergency; and (3) the FDA commissioner, NIH director, and CDC director must consult with each other. Stuart L. Nightingale, Joanna M. Prasher & Stewart Simonson, *Emergency Use Authorization (EUA) to Enable Use of Needed Products in Civilian and Military Emergencies, United States*, 13 EMERGING INFECTIOUS DISEASES 1046, 1046, 1048 (2007), available at <http://www.cdc.gov/117/pdfs/1046.pdf>.

frameworks. It then separately discusses emerging therapeutic vaccines for transmittable diseases, as they present a unique scenario.

A. The Utilitarian Framework

Utilitarianism is based on the simple goal of maximizing the greatest good for the greatest number, which requires the consideration of consequences. Because “the most significant benefits of [prophylactic] vaccination are related to protection of others,”⁵⁶ the use of prophylactic vaccines to achieve overall health maximization across socio-economic and geographic demographics is well-grounded in utilitarian principles. Utilitarians engage in a cost-benefit analysis to maximize health outcomes in the long run; the monitoring of vaccines “should consider more than just the immediate effects on vaccine efficacy.”⁵⁷ Among the relevant long-term costs of partially effective vaccines are the risks of virulence evolution and of chilling the progress of research.

1. Possible Virulence Evolution of Pathogens

The first long-term cost of using partially effective vaccines is the possibility that, in response, pathogens may evolve into more virulent strains.⁵⁸ Such an evolutionary change could create more harm than good. The evolution of pathogens, though, is uncertain and determined, to some extent, by host-specific characteristics.⁵⁹ Several studies measuring or predicting virulence evolution in response to vaccination have found that some vaccines may indeed cause pathogens to evolve into more virulent strains.⁶⁰ The implications of

56. May, *supra* note 1, at 408.

57. Tom Smith, *Imperfect Vaccines and Imperfect Models*, 17 *TRENDS IN ECOLOGY & EVOLUTION* 154, 154 (2002).

58. *See generally* Sylvain Gandon, Margaret J. Mackinnon, Sean Nee & Andrew F. Read, Letter, *Imperfect Vaccines and the Evolution of Pathogen Virulence*, 414 *NATURE* 751, 751–56 (2001).

59. *See, e.g.*, Jean-Baptiste André & Sylvain Gandon, *Vaccination, Within-Host Dynamics, and Virulence Evolution*, 60 *EVOLUTION* 13, 13 (2006) (explaining virulence evolution in different types of hosts).

60. *See id.* (“[V]accination may promote the evolution of faster replicating and, consequently, more virulent strains.”); *see also* Sylvain Gandon, Margaret Mackinnon, Sean Nee & Andrew Read, *Imperfect Vaccination: Some Epidemiological and Evolutionary Consequences*, 270 *PROC. R. SOC. LOND. B.* 1129, 1135 (2003) (“Our model predicts that an anti-growth component of host resistance may select for higher parasite virulence.”); Vitaly V. Ganusov & Rustom Antia, *Imperfect Vaccines and the Evolution of Pathogens Causing Acute Infections*

higher pathogen virulence are two-fold: (1) at the individual level, unvaccinated hosts would be exposed to more dangerous pathogens; and (2) at the population level, “evolution would erode the benefits of vaccination.”⁶¹

For example, there are concerns about evolving pathogen virulence with malaria.⁶² Malaria is a parasitic disease spread by mosquitoes and is currently one of the largest global health concerns.⁶³ The malaria disease creates a large social and economic burden on society and is correlated with higher poverty and slower economic growth.⁶⁴ “The determinants of virulence in malaria[, however,] are [still] not well understood.”⁶⁵ Currently, there is no effective malaria vaccine available, and potential vaccines in development are in clinical trial phases.⁶⁶ One study explored the virulence evolution of malaria by using a laboratory model of the rodent malaria species, *Plasmodium chabaudi*, and examining field data for the human malaria species, *Plasmodium falciparum*.⁶⁷ The researchers concluded that “parasite populations [of malaria] are expected to evolve new levels of virulence in response to medical interventions such as vaccines.”⁶⁸

However, not all vaccines may result in virulence evolution. The scientific consensus is that anti-toxin and anti-growth vaccines may select for higher virulence, as may “vaccines which block transmission of pathogens . . . by reducing the strength of . . . intrahost

in Vertebrates, 60 *EVOLUTION* 957, 957 (2006) (“[T]he use of either antigrowth or antitransmission vaccines leads to the evolution of pathogens with an increased within-host growth rate; infection of unvaccinated hosts with such evolved pathogens results in high host mortality and low pathogen transmission.”).

61. Margaret J. Mackinnon & Andrew F. Read, *Virulence in Malaria: An Evolutionary Viewpoint*, 359 *PHIL. TRANS. R. SOC. LOND. B.* 965, 973 (2004).

62. *See id.*

63. *See Global Health: Malaria Overview*, KAISER FAMILY FOUND., <http://globalhealth.kff.org/Diseases/Malaria.aspx> (last visited Oct. 26, 2012) (describing the state of malaria in the global health context and how international efforts to address the disease have intensified in recent years).

64. There are 300 million to 500 million cases of malaria worldwide each year, causing at least 1 million deaths annually. Jeffrey Sachs & Pia Malaney, *The Economic and Social Burden of Malaria*, 415 *NATURE* 680, 680–83 (2002).

65. Smith, *supra* note 57, at 154.

66. *See The State of Global Malaria Vaccine Development*, MALARIA VACCINE INITIATIVE, <http://www.malariaivaccine.org/malvac-state-of-vaccine-dev.php> (last accessed Nov. 1, 2012).

67. Mackinnon & Read, *supra* note 61, at 966–72.

68. *Id.* at 965.

competition between unrelated pathogen strains.”⁶⁹ Anti-toxin and anti-growth vaccines, such as the “blood stage” malaria vaccines currently in development, do not prevent host infection but instead slow parasite growth.⁷⁰ With these vaccines, “[c]ompetition among parasites leads to selection of more virulent parasites, because the faster growing parasites corner the resources of the host for themselves, pulling the evolutionarily stable state further towards virulence than in the situation without competition.”⁷¹ On the other hand, anti-infection and anti-transmission vaccines that do *not* affect intrahost pathogen competition “have no [virulence evolution] effects . . . because their transmission-blocking effects . . . do not alter the [evolutionary] costs and benefits of virulence.”⁷² Thus, certain types of vaccines are more prone than others to virulence evolution that could offset the benefits of vaccination.

2. Possible Perverse Research Incentives

The second long-term cost of using partially effective vaccines is that if they are profitable, they may discourage or disincentivize pharmaceutical companies from developing more effective vaccines. However, there is some evidence that demand in the market may respond efficiently to partially effective vaccines, providing market incentives to continue developing more effective vaccines. For instance, demand for an 80% effective malaria vaccine in any given year is estimated to be more than twice that for a 50% effective vaccine.⁷³ Whether this positive correlation between efficacy and demand applies generally to all vaccines is less clear. Further economic analysis is needed to determine how much of an increase in demand is sufficient to compel a manufacturer to develop an even more effective vaccine.

69. Ganusov & Antia, *supra* note 60, at 965-68; Mackinnon & Read, *supra* note 61, at 973; *see also* Gandon, Mackinnon, Nee & Read, *supra* note 60, at 1135; Smith, *supra* note 57, at 155.

70. Mackinnon & Read, *supra* note 61, at 972-73; Smith, *supra* note 57, at 155.

71. Smith, *supra* note 57, at 155.

72. Mackinnon & Read, *supra* note 61, at 973.

73. *See* Boston Consulting Group, Meeting Handout, Market Assessment of Malaria Vaccines 85 (Jan. 19, 2005), *available at* http://www.malariavaccine.org/files/Market-Assessment-18Jan05-LB-BOS_000.pdf.

B. Partially Effective Vaccines in Light of Deontological Principles

In addition to a cost-benefit utilitarian analysis, several deontological principles—beneficence, justice and autonomy—are also salient in the use of partially effective vaccines.⁷⁴

1. Beneficence: Contributing to the Welfare of Others

The deontological notion of beneficence holds that people should contribute to the welfare of others if doing so does not impose an undue burden.⁷⁵ Vaccines—even partially effective ones—that confer benefits to others satisfy the value of beneficence because they confer third party benefits with little risk of harm to the recipient—the “discomfort, time, money, and risk of getting [a] disease from a bad batch of [a] vaccine” are relatively low costs compared to the social benefits to others.⁷⁶

2. Justice: Vaccine Accessibility for Groups at High Risk

Another deontological principle, justice, calls for scarce resources to be allocated fairly.⁷⁷ It is an unfortunate reality that vaccines are not equally available to all individuals. Populations in developing countries often do not enjoy access to the newest and most effective vaccines, and those with little or no health insurance, in the United States, may be effectively barred from obtaining certain vaccinations as well.⁷⁸ Other factors include location and knowledge—people living in rural or difficult-to-reach places and those unaware of vaccinations, often have limited access to vaccines.⁷⁹ It may seem inherently unjust if some—especially groups at high risk for a disease—must settle for relatively less effective vaccines if more effective ones exist.

However, the availability of partially effective vaccines as an option may actually be beneficial for the sake of vaccine accessibil-

74. BEAUCHAMP & CHILDRESS, *supra* note 9, at 352.

75. *Id.* at 167-68.

76. JOSEPH E. STIGLITZ, *ECONOMICS OF THE PUBLIC SECTOR* 120 (1988).

77. BEAUCHAMP & CHILDRESS, *supra* note 9, at 352–58.

78. *See, e.g.*, Grace M. Lee et al., *Gaps in Vaccine Financing for Underinsured Children in the United States*, 298 J. AM. MED. ASS'N 638 (2007).

79. *See, e.g.*, Sebahat D. Torun & Nadi Bakirci, *Vaccination Coverage and Reasons for Non-Vaccination in a District of Istanbul*, 6 BMC PUB. HEALTH 125 (2006).

ity. Data shows that the degree of vaccine efficacy may significantly shift the demographics of market demand. For example, demand for an 80%-effective malaria vaccine could be as high as 154 million individuals in 2025.⁸⁰ Significant uptake (63% of demand) of an 80%-effective vaccine would be from *outside* of Africa, where the vast majority of malaria cases occur.⁸¹ On the other hand, if a malaria vaccine were only 50% effective, then over 60% of demand would be from *within* Africa.⁸² Thus, allowing partially effective vaccines on the market may help keep prices low in certain regions and actually increase accessibility for those at highest risk of infection. This market effect would be especially beneficial for diseases that disproportionately affect third world countries.

3. Autonomy: Allowing for Patient and Provider Choice

Finally, partially effective vaccines satisfy the deontological principle of autonomy. Under the rule of autonomy, “competent adults should be free to determine their own behavior, including the acceptance or refusal of medical interventions.”⁸³ Deontologists would uphold an ethical obligation to provide the full range of vaccine options available, regardless of their efficacy. This notion competes with the utilitarian framework, as it does not consider the potential consequences of allowing patients and physicians to voluntarily choose a relatively ineffective vaccine. Due to imperfect knowledge and the free-rider problem, physicians and patients may choose vaccines based on their cost rather than their expected benefits to others.⁸⁴ There is also the potential for undue, outside influence; for instance, insurance companies might encourage the administration of lower efficacy vaccines through higher reimbursement or lower patient cost-sharing. Nevertheless, making partially effective vaccines available expands the range of choices accessible to patients and phy-

80. Boston Consulting Group, *supra* note 73.

81. *Id.*; see also *Global Health: Malaria Overview*, *supra* note 63 (“More than 80% of [malaria] cases and almost 90% of deaths occurred in Africa in 2008 . . .”).

82. *Id.*

83. Field & Caplan, *supra* note 10; see also BEAUCHAMP & CHILDRESS, *supra* note 9, at 351.

84. See STIGLITZ, *supra* note 76, at 120 (“In many cases, the private costs exceed the private benefits, but the social benefits . . . far exceed the costs. Because of the free rider problem, governments frequently require that individuals become vaccinated.”).

sicians. The potential dangers of doing so may be addressed through health policy reform, which is discussed in Part III.

C. An Emerging Category of Vaccines: Therapeutic Vaccines

Vaccines have traditionally been prophylactic against contagious diseases, but many are now therapeutic, meaning they have the ability to reduce severity of a disease or infection rather than prevent it.⁸⁵ These vaccines are being developed for diseases that “do not require widespread immunization to establish herd immunity and prevent outbreaks,” like cancer and certain sexually transmitted infections (“STIs”).⁸⁶ From a public health standpoint, many would not be “medically necessary” to prevent the spread of disease.⁸⁷ As a result, therapeutic vaccines merit additional ethical consideration.

There are worries that recipients of therapeutic vaccines for transmittable diseases might gain a false sense of protection. The benefits of vaccination may disappear if individuals engage in more risky behavior after receiving such vaccines.⁸⁸ Several studies have been conducted to estimate the extent of post-vaccination risk-seeking behavior, and thus far, the data is inconclusive.

For example, many post-vaccination behavioral studies have tried to predict the potential effects of a partially effective vaccine for HIV.⁸⁹ Ideally, an HIV vaccine would afford immunity, but “[a] more realistic goal [has been] to develop a vaccine that . . . prevents . . . clinical disease progression.”⁹⁰ All of the potential HIV

85. See, e.g., Jon Cohen, *Vaccines Get a New Twist*, 264 SCI. 503 (1994) (describing the emergence of new types of vaccines, including treatment vaccines); see also Steven A. Rosenberg, James C. Yang & Nicholas P. Restifo, *Cancer Immunotherapy: Moving Beyond Current Vaccines*, 10 NATURE MED. 909 (2004) (discussing new cancer vaccines that focus on tumor regression).

86. Note, *Toward a Twenty-First-Century: Jacobson v. Massachusetts*, 121 HARV. L. REV. 1820, 1828 (2008).

87. *Id.*

88. See *id.*

89. See, e.g., *id.*; see also Kyeen M. Andersson et al., *Predicting the Impact of a Partially Effective HIV Vaccine and Subsequent Risk Behavior Change on the Heterosexual HIV Epidemic in Low- and Middle-Income Countries: A South African Example*, 46 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 78, 78 (2007); Sally M. Blower et al., *Predicting the Potential Public Health Impact of Disease-Modifying HIV Vaccines in South Africa: The Problem of Subtypes*, 5 CURRENT DRUG TARGETS—INFECTIOUS DISORDERS 179, 179 (2005).

90. Angelique A.C. Lemckert, Jaap Goudsmit & Dan H. Barouch, Review, *Challenges in the Search for an HIV Vaccine*, 19 EUR. J. EPIDEMIOLOGY 513, 513 (2004).

vaccines in development around the world are such disease-modifying vaccines—they do not prevent infection, but instead aim to increase survival.⁹¹

One study modeled the effect of a partially effective vaccine on HIV prevalence in Bangkok, Thailand and found that a 75%-effective HIV vaccine would lead to a forty-year incidence rate of 37% in Bangkok, compared to 50% without vaccination.⁹² The study also warned, however, that if 90% of the people who receive a 30% effective vaccine engage in higher risk behavior post-vaccination, then the benefits of vaccination would disappear.⁹³ Another study predicted that in South Africa, “a 40% effective HIV vaccine would avert 61,000 infections and reduce future HIV prevalence from 20% to 13%.”⁹⁴ Similar to the Bangkok study, the South African study found that increased risk behavior combined with a less-than-43% effective vaccine, though, might actually *worsen* the HIV epidemic.⁹⁵ Even so, the empirical data thus far does not show “unequivocal support for the hypothesis that participants’ risk behaviour generally increases” after partially effective vaccination.⁹⁶ And even if there is such a tendency, it might be alleviated with educational programs or warnings to accompany partially effective vaccinations.

In the end, “[g]iven the urgent need for an HIV vaccine,” there are calls to make one available, even if it is only partially effective.⁹⁷ “Even modestly effective HIV vaccines can confer enormous benefits in terms of HIV infections averted and decreased HIV prevalence . . . [, but] programs to reduce risk behavior may be important components of successful vaccination campaigns.”⁹⁸ Thus, to attain

91. Blower et al., *supra* note 89, at 179.

92. See Elizabeth Bogard & Karen M. Kuntz, *The Impact of a Partially Effective HIV Vaccine on a Population of Intravenous Drug Users in Bangkok, Thailand: A Dynamic Model*, 29 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 132, 139–40 (2002) (assuming a 5% probability of post-vaccination risk behavior increase).

93. *Id.*

94. Andersson et al., *supra* note 89, at 78.

95. *Id.*

96. Catherine Slack et al., *Provision of HIV Treatment in HIV Preventive Vaccine Trials: A Developing Country Perspective*, 60 SOC. SCI. & MED. 1197, 1199 (2005).

97. Andersson et al., *supra* note 89 (predicting that “vaccines with only partial efficacy are likely to be used initially in populations at high risk for HIV infection”).

98. *Id.*

the benefits of therapeutic vaccines for transmittable diseases, it may be necessary to design programs that minimize harmful risk-seeking behavior post-vaccination. This approach would be aligned with the utilitarian framework for overall maximization of health benefits.

III. The Need for Reform in Light of Partially Effective Vaccines

As the ethical considerations above show, partially effective vaccines are generally desirable. However, there remain outstanding concerns that need to be addressed over time with policy and regulatory reform. This Part proposes that Congress and the FDA establish a system of reinforcing regulatory standards and policies to promote comparative effectiveness research, mandate post-approval clinical trials, and track the long-term effectiveness of vaccines. The Patient Protection and Affordable Care Act (“ACA”)⁹⁹ begins to implement some of these ideas, but more is needed.

A. Research Incentives Through Comparative Effectiveness Requirements or Government Subsidies

To counteract the possibility of reduced research incentives, the FDA could add a requirement for comparative effectiveness data, such as efficacy relative to other vaccines, vaccine combinations, or patient subpopulations, prior to market approval. For example, a proposition has been made by some to require manufacturers to include information about comparative effectiveness on labeling and marketing materials.¹⁰⁰ Such a requirement would encourage vaccine manufacturers to compete on comparative effectiveness and to study vaccines in more targeted patient subgroups.

In addition, where market incentives are insufficient, the government could provide subsidies for research to improve the efficacy of vaccines already on the market. Given that the vaccine manufacturing industry is relatively small,¹⁰¹ it would be conceivable for the

99. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

100. See, e.g., Randall S. Stafford, Todd H. Wagner & Philip W. Lavori, *New, but Not Improved? Incorporating Comparative-Effectiveness Information into FDA Labeling*, 361 NEW ENG. J. MED. 1230, 1230–33 (2009).

101. See *Losing Momentum: Are Childhood Vaccine Supplies Adequate? Hearing Before the Subcomm. on Pub. Health of the S. Comm. on Health, Educ., Lab. & Pensions*, 107th Cong. 2 (2002) (statement of Sen. Jack Reed, explaining

government to direct financial incentives to the appropriate parties. Large non-profits, such as the Bill and Melinda Gates Foundation, could also incentivize continued research by contracting purchase guarantees with manufacturers for more effective vaccines.¹⁰²

B. A Stronger Commitment to Long-Term and Comparative Effectiveness Research

A related strategy to mitigate the long-term risks of partially effective vaccines is to require continued efficacy studies after FDA approval. For instance, the European Medicines Agency, the agency responsible for scientific evaluation of pharmaceutical products for use in the European Union, emphasizes efficacy studies *after* vaccine approval:

It may not be possible or appropriate . . . to conduct studies to estimate vaccine effectiveness since co-ordinated regional or national networks may be necessary to ensure that cases are reliably detected. However, applicants should discuss arrangements for ongoing disease surveillance and the potential for estimating effectiveness with appropriate public health authorities in countries where the product is to be used and where reliable surveillance systems are in place.¹⁰³

Under the FDC Act, the FDA can require post-marketing Phase IV trials for certain purposes, like continued monitoring of safety and efficacy.¹⁰⁴ For instance, approval of the HPV vaccines Gardasil and Cervarix were conditioned on the future submission of trial data on spontaneous abortions in vaccine recipients.¹⁰⁵ The FDA also condi-

that only four manufacturers produce nearly all pediatric vaccines available in the United States).

102. See Michael Kremer, *A Purchase Commitment for Vaccines*, in GLOBAL PUBLIC GOODS FINANCING 37 (2002). The intricacies of vaccines and research incentives are outside the scope of this paper. For a general overview of the topic, see MICHAEL KREMER & RACHEL GLENNERSTER, *CREATING INCENTIVES FOR PHARMACEUTICAL RESEARCH ON NEGLECTED DISEASES* (2004); Richard A. Jenkins et al., *Incentives and Disincentives to Participate in Prophylactic HIV Vaccine Research*, 9 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES & HUMAN RETROVIROLOGY: CLINICAL SCI. 36 (1995).

103. Comm. for Medicinal Prods. for Human Use, European Meds. Agency, *Guideline on Clinical Evaluation of New Vaccines*, at 14, (Oct. 16, 2006), available at <http://www.tga.gov.au/docs/pdf/vwp/16465305enfin.pdf>.

104. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 505 (2006) (providing for post-approval evaluation and mitigation strategies for safety and effectiveness).

105. Dept. of Health & Human Services, *Approval Letter—Human Papillomavirus Quadrivalent (Types 6,11,16,18) Vaccine, Recombinant* (June 8,

tioned the approval of Gardasil on the submission of studies on the duration of immunity conferred by the vaccine¹⁰⁶ and of Cervarix on submission of data from five ongoing long-term efficacy trials.¹⁰⁷

While post-marketing Phase IV trials could be an important step toward long-term efficacy research, there has not been a strong commitment to them. No drug or vaccine has ever been withdrawn from the market for failure to meet post-marketing commitments, despite a 2005 report by the FDA that found that only 9.6% of open post-marketing commitments had been met.¹⁰⁸ Thus, the FDA's requirement of post-marketing trials has not been seriously enforced and needs to be given more teeth to obtain the desired compliance.¹⁰⁹

One developing initiative provides some reason for optimism. The ACA established the Patient-Centered Outcomes Research Institute ("PCORI") in September 2010, with the aim of prioritizing, promoting and publicizing comparative effectiveness research ("CER").¹¹⁰ Interest in CER has been growing for at least a couple of decades, beginning with the National Center for Health Care Technology (disbanded in 1981) and continuing more recently with \$1.1 billion in CER funding as part of the American Recovery and Reinvestment Act.¹¹¹ PCORI, however, is the first time the U.S. government has established and funded an independent institute tasked with "identifying national research priorities for CER" and "carrying out a research project agenda" through a transparent process, including public comment periods prior to publication of findings.¹¹²

2006), available at <http://www.fda.gov/ApprovedProducts/ucm111283.htm>; Dept. of Health & Human Services, *Approval Letter—Cervarix* (Oct. 16, 2009), available at <http://www.fda.gov/BiologicsBloodVaccines/ApprovedProducts/ucm186959.htm>.

106. Approval Letter—Human Papillomavirus Quadrivalent (Types 6,11,16,18) Vaccine, Recombinant, *supra* note 105.

107. Approval Letter—Cervarix, *supra* note 105.

108. DEP'T OF HEALTH AND HUMAN SERVICES, Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies, 70 Fed. Reg. 33, 8379–81 (Feb. 18, 2005).

109. Wood, *supra* note 43, at 621.

110. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, § 6301, 124 Stat. 727–743 (codified as amended at 42 U.S.C. §§ 299b-37, 1320e, 1320e-1, 1320e-2, 26 U.S.C. §§ 9511, 4375 (2010)); see also Raj Sabharwal et al., *What Is Comparative Effectiveness Research and What Will It Mean for Patients, Physicians, and Payors?* CTR. FOR MED. TECH. POLICY (2010).

111. See Sabharwal et al., *supra* note 110, at 2–3.

112. See *id.* at 3–4. It is important to note that PCORI represents a compromise between those pushing for value-based medical care and those

PCORI provides an opportunity to identify important data gaps in vaccine efficacy and evidence-based knowledge, including after FDA approval. It can promote the importance of smaller-scale, long-term observational research and integrative systemic studies on patient subgroups or combinations of vaccines. Moreover, it can focus on CER and produce valuable data when alternatives to partially effective vaccines exist.

The newly established PCORI pushes clinical research and health care assessment in the right direction. It represents a potential emphasis on CER and provides a process for prioritizing health care research in general. However, it remains to be seen how much emphasis PCORI places on vaccines and whether it is enough to promote a comparative understanding of them. It will be a challenge for PCORI, which cannot issue guidelines or recommendations, to prioritize areas of research and then effectively disseminate such information to providers, patients and payers.

Ultimately, even if PCORI places an emphasis on vaccine CER, additional policies and regulations may need to be implemented. The FDA, for one, should take steps to make vaccine approvals contingent on a more stringently enforced requirement to submit favorable Phase IV results post-approval.

C. A VAERS-Like Effectiveness Reporting System

One final way to ensure continued understanding of vaccine efficacy is to implement a reporting system in addition to the proposed research-based initiatives. Encouraging or requiring health providers to follow up on patients and report cases of partial- or non-responders to the Advisory Committee on Immunization Practices (“ACIP”)¹¹³

concerned that such research could be biased or could lead to rationing, or so-called “Death Panels.” Sean R. Tunis & Steven D. Pearson, *U.S. Moves to Improve Health Decisions*, 341 *BRIT. MED. J.* 431, 431–32 (2010). As a result, PCORI’s independent 21-member board includes stakeholders from provider, patient, payer, manufacturer, quality improvement, and researcher groups; it cannot issue practice guidelines or recommendations; and Medicare and Medicaid cannot make coverage or payment decisions based solely on PCORI’s findings. *Id.*

113. “The ACIP is a group of medical and public health experts that develops recommendations on how to use vaccines to control disease in the United States.” *The Advisory Committee on Immunization Practices*, CTRS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-acip-color-office.pdf> (last updated Mar. 2012). It develops, among

can ensure the availability of more centralized and complete data on effectiveness.

In the United States, the ACIP currently reviews vaccine efficacy data to make recommendations on vaccination schedules, but beyond that, there is little emphasis on post-approval effectiveness.¹¹⁴ This anomaly is in contrast to the system in place for reporting vaccine *safety* issues, the Vaccine Adverse Event Reporting System (“VAERS”).¹¹⁵ The VAERS post-vaccination surveillance program, developed by the FDA and the Center for Disease Control and Prevention (“CDC”), allows anyone—patients, parents or physicians—to report adverse events related to vaccines.¹¹⁶ VAERS serves to both monitor vaccine lots and identify possible new adverse events.¹¹⁷ Reported data can notify the FDA of defective vaccine lots so that suspect vaccines can be quickly pulled from the market.¹¹⁸ Also, if the same adverse event is reported by many people, the scientific community can develop hypotheses regarding causality and design laboratory studies to further investigate safety issues.¹¹⁹

A similar post-approval program could be applied in the context of vaccine effectiveness, and perhaps it could even be incorporated into the existing VAERS framework and provide further data for evidence-based decision-making. There is already a trend toward using evidence-based decision-making to determine the efficacy of vaccines relative to cost.¹²⁰ The ACIP and CDC are starting to engage in cost-utility analyses to make immunization recommendations and schedules; for example, the ACIP amended its immunization schedule for the MCV4 meningitis vaccine in October 2010 after reviewing new health economics data.¹²¹ Additionally, a vaccine effectiveness

other guidelines, vaccination schedules and appropriate dosage recommendations.
Id.

114. *Id.*

115. VAERS is a “post-marketing safety surveillance program” sponsored by the CDC and FDA, collecting information about adverse events and side effects after the administration of licensed vaccines in the United States. *Vaccine Adverse Event Reporting System*, VAERS, <http://vaers.hhs.gov/index> (last visited Nov. 1, 2012).

116. Stehlin, *supra* note 24, at 3.

117. *Id.* at 4.

118. *Id.*

119. *Id.*

120. *See generally* Field & Caplan, *supra* note 10.

121. DEP’T OF HEALTH AND HUMAN SERVICES, Summary Report by the Advisory Committee on Immunization Practices (ACIP) (Oct. 27-8, 2010),

reporting system has the benefit of generating patient data that PCORI can use, since PCORI can set an agenda for observational and systemic studies that integrate existing data. Therefore, it would be important for any effectiveness reporting system to be set up collaboratively, with the roles of PCORI, the ACIP, and the CDC in mind.

In sum, policy and regulatory reform will be necessary to ensure and promote understanding of the desirability and long-term costs of partially effective vaccines. The ACA's establishment of PCORI takes the first steps toward these goals. However, it will be important to continue developing a stronger policy and regulatory framework for vaccine efficacy so that the ethical administration of partially effective vaccines can be evidence-based and informed.

Conclusion

Many emerging vaccines are partially effective and thus pose a dilemma between (1) permitting urgently needed vaccines to enter the market, and (2) doing so with less-than-complete risk-benefit knowledge. The use of partially effective vaccines poses ethical issues regarding fair accessibility, physician and patient decision-making, long-term health risks and incentives for future research. In addition, new therapeutic vaccines for transmittable diseases pose concerns about post-vaccination risk-seeking behavior.

As new partially effective vaccines emerge, the need to update and supplement the FDA's efficacy requirement will become increasingly important. Comparative research and post-marketing studies should become more important to understanding the costs and benefits of partially effective vaccines. Already, the ACA has established PCORI, an independent institute dedicated to identifying and promoting research on health care strategies and treatments, especially through comparative effectiveness research. It remains to be seen, though, how PCORI will impact the standard for vaccine efficacy. Additional policy and regulatory reforms may be required, including new research incentives, a stronger commitment to long-term and comparative effectiveness research, and the implementation of an effectiveness reporting system.

Therefore, the emerging landscape of partially effective vaccines calls for an updated framework for vaccine efficacy—one that will promote comparative effectiveness research, mandate post-approval clinical trials and track long-term effectiveness without hindering the entrance of urgently needed vaccines.