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Vaccines and Ethics

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FROM THE EDITOR
Vaccination: A Victim of Its Own Success

"Vaccination is the medical sacrament corresponding to baptism."
Samuel Butler

My grandfather Robert is a stalwart American man of letters, a role model with a taciturn temperament known for his inventive wit and experiential wisdom. As a child I hung on his every word and imagined him walking and talking in the black and white world of his photographs. One afternoon his rough voice softened as he recounted the day he lined up with hundreds of his neighbors outside a local hospital to receive Salk's inactivated polio vaccine. He paused and looked up, recalling that as he received the injection, children inside the hospital lay immobilized in iron lungs. I watched his blue eyes shimmer, revealing a memory powerful enough to evoke this reaction from a stoic.

The eradication of the crippling lower motor neuron degeneration and subsequent flaccid paralysis of poliomyelitis is perhaps the best recent example of a supremely successful vaccination campaign. The World Health Organization estimates that 8 million people who would otherwise have been paralyzed by polio are walking because they were immunized. Today entire generations are free from the fear of polio, yet we struggle with, on the one hand, the fear of new diseases and, on the other, with fear of vaccines themselves.

This month's issue of *Virtual Mentor* examines the past, present, and future of vaccination medicine and ethics. Today the tribulations of diseases such as smallpox and polio are but fading shadows of history, yet new challenges in vaccination arise every day. Lack of clarity about the safety and efficacy of vaccination have sparked intense debate within the international medical community and extensive public suspicion in recent years.

In this month's issue, we address several questions that are germane to all of us who counsel patients about vaccines: How—and why—is misinformation propagated, and why does it find such wide acceptance? How can we educate individual patients and the public so that they can differentiate the science from the rhetoric about vaccines? How will we manage future vaccine shortages? How should we approach first-in-human vaccine clinical trials? Who bears the burden of responsibility when vaccines inevitably cause an adverse event? Should we embrace future "vaccinations" that target the brain, specifically normal stress responses? Why should we risk the side effects of a vaccine when regular checkups can screen for disease instead of trying to prevent it?

There is one individual story that, for me, answers this last question particularly well. By the time of her diagnosis in 2003, District Attorney Cheryl Lieck had never missed a well checkup in her life. She trusted her long-time gynecologist's reports of her regular pap smears, though she had symptoms that were troubling. After she sought out another doctor, the root of her symptoms was revealed—cervical cancer.

Over the next few years, Cheryl waged a successful battle, but at a high cost. She underwent cervical cauterization, cold knife cone surgery, a hysterectomy, oophorectomy, and lymph node removal. She made a 120-mile trip every weekday for 6 weeks of radiation.

Today Cheryl is symptom-free in remission and credits the support of her family, friends, and doctors with saving her life. Cheryl recently asked her doctor about the HPV vaccine for her children and concluded, "It's a no-brainer. We teach our kids to wear their seatbelts [even though] nobody plans on having their children in a car crash."

One of the many difficulties for medical professionals involves talking to parents about their teenagers' sexual activity. As Cheryl puts it, "Parents can't do everything, but when you have the power to prevent something from happening, you do it!"

We question the value of vaccines because they have become a victim of their own success, so it is an imperative that we educate ourselves with objective, fact-based information to weigh the benefits and risks of vaccination. Will cervical cancer, measles, and HIV eventually go the way of polio? Perhaps one day I will sit down with my grandson and tell him of our generation's success.

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CLINICAL CASE
The HPV Vaccine and Parental Consent
Commentary by Donna T. Chen, MD, MPH, Lois L. Shepherd, JD, Daniel M. Becker, MD, MPH, MFA

As pediatrician Dr. Carson completes her physical exam of Alex, a healthy 15-year-old girl, she senses that Alex has something else on her mind. “Alex, I’m happy to say that you’re in perfect health. Do you have any more questions for me before we bring your mother back into the room?”

“My boyfriend and I are thinking about having sex,” Alex responds. “I’ve never had sex before.” Dr. Carson asks a few more questions, reviews safe sex practice and provides prophylactic condoms. “You should also know that the CDC recommends the HPV vaccine to girls starting at age 11 to prevent infections that may one day cause cancer.” Dr. Carson continues to describe the vaccine’s efficacy, prevalence, and known side effects. Alex decides she would like to receive the vaccine.

Dr. Carson asks Alex’s mother to re-enter the room and begins to discuss the recommendation for the HPV vaccine. Alex’s mother objects. “The HPV vaccine is mandated here in Virginia for 11-year-old girls. I would have chosen to opt out of the mandate because I don’t want my daughter to act irresponsibly or suffer unknown side effects.”

Alex responds angrily. “I’ll come back to Dr. Carson’s office alone, or get the vaccine at Downtown Family Planning,” she says, referring to a Title-X clinic near where they live in Richmond. Dr. Carson believes that, although physicians can legally provide both reproductive health care and STI diagnosis and treatment to a competent minor, they cannot legally administer the HPV vaccine without parental consent.

Commentary
Pediatricians, family physicians, and ob-gyns who routinely care for adolescent girls will be familiar with many of the ethical and practical challenges that Dr. Carson faces in this office visit: confidentiality, access to health care, consent, and conflicts between public health policy and personal health beliefs. Walking through this vignette, with stops for discussion along the way, we review some of these common challenges while addressing unique features added by the HPV vaccine.

“Do you have any more questions for me before we bring your mother back into the room?”

By providing Alex an opportunity to discuss matters privately, Dr. Carson follows a recommended practice for gaining the trust of adolescent patients—a practice that is supported by ethical principles, legal analyses, and research findings [1, 2]. "Time alone" has been shown to significantly increase the likelihood that adolescents will discuss sensitive health matters and is generally supported by parents and appreciated by patients [1-3].

"My boyfriend and I are thinking about having sex," Alex responds. "I've never had sex before." Dr. Carson asks a few more questions, reviews safe sex practice and provides prophylactic condoms.

Alex has responded by bringing up a sensitive health issue, offering Dr. Carson an important opportunity to provide information and preventive health recommendations.

Because many adolescent patients see their primary care physicians infrequently and at those times for acute matters only, opportunities to provide preventive health care can be few and far between [2, 4]. In our clinical case scenario, Alex has come to Dr. Carson for a physical exam. We'd expect Dr. Carson to allow "time alone" for Alex to bring up sensitive matters, but we'd also expect Dr. Carson to ask about sexual health in a way that sets the stage for current and future discussions. Note that as the conversation progresses, Dr. Carson misses an opportunity to find out what Alex has discussed with her mother and how they should bring her mother into the discussion. Recognizing and negotiating this tripartite relationship is critical to best practices for adolescents [1, 2].

Reproductive health care and diagnosis and treatment of sexually transmitted infections (STIs) are important topics when adolescents go to the doctor. However, the types of services that can be offered without parental consent or knowledge vary considerably from state to state [5]. Some states allow minors to consent to all forms of medical treatment as long as the minor meets specified criteria set by law (e.g., particular age, married, high school graduate). There are also specific statutory exemptions, varying by state, that allow minors to receive certain kinds of medical services without parental consent or knowledge (e.g., family planning, testing and treatment for STIs, mental health care, and/or substance abuse counseling).

So far, Dr. Carson is likely to be within the ethical and legal bounds of adolescent care and confidentiality in most states, although practitioners should take care to know the law of the state in which they practice. The law can contain unexpected gaps and incongruities. For example, in Virginia, where Dr. Carson practices and Alex lives, minors can consent to the kinds of medical services listed above in parentheses. At the same time, Virginia parents have a right to obtain their child's health records unless the disclosure of those records would be reasonably likely to cause substantial harm to the minor or another person [6]. As a result, in some circumstances parental permission and knowledge might be avoided initially, but the minor patient's privacy and confidentiality may not be entirely protected.

In the clinical scenario under discussion the possibility of inadvertent disclosure should prompt Dr. Carson to take extra care when recording information in Alex's medical record—better to document the conversation with Alex in a general way than to reveal what Alex confided about her boyfriend. Physicians should also be mindful of the fact that regardless of laws that might protect minors' confidentiality against disclosure to parents, "explanation of benefits" in insurance statements sent to parents may specify the medical services for which a claim is made [1, 7]. While this is not an issue with respect to advice about safe sex practices and the provision of condoms, it would be relevant if reimbursement were sought for other services such as laboratory testing for sexually transmitted infections.

"You should also know that the CDC recommends the HPV vaccine to girls at age 11 to prevent infections that may one day cause cancer."

Chronic infection with high-risk human papillomavirus (HPV) causes almost all cancer of the cervix. Condoms are only partially effective in preventing HPV transmission. Two vaccines are available: Gardasil, a quadrivalent vaccine, targets HPV strains 6, 11, 16, and 18; Cervarix, a bivalent vaccine, targets strains 16 and 18. Large clinical trials as well as epidemiological studies have demonstrated vaccine effectiveness in preventing genital warts, precancerous lesions, throat cancer, and anal cancer as well as cervical cancer [8-10].

HPV vaccines are more effective if administered before sexual debut and therefore before HPV infection. While the median age of first sexual intercourse in the U.S. is 17 years, 13 percent of girls engage in sexual activity before age 15 and 4 percent before age 13 [11]. In 2007 the CDC recommended that the three-dose schedule of the HPV vaccine be given to girls aged 11-12, and catch-up vaccination to girls and women aged 13-26 years.

Until recently male transmission of HPV was not factored into national vaccine policy. In 2009 Gardasil was approved for boys aged 9-26 years, and in October 2011 the CDC added routine HPV vaccination for boys aged 11-12 and a catch-up vaccine for boys and men aged 13-21. Some experts would give the catch-up vaccine to men as old as 26. Vaccinating boys and men may reduce rates of anal and throat cancer in men and also reduce cancer in women by reducing HPV transmission [12]

Dr. Carson provides an important service in discussing the HPV vaccine with Alex, although one has to wonder why the vaccine was not discussed during earlier visits with Alex and her parents, either as a part of a "well adolescent" visit or as part of routine review of recommended vaccines. Such reviews are an integral part of adolescent health care, as patients may need to "catch up" on vaccinations usually administered to children and also need to be informed about new vaccines. For example, three "new" vaccines have been licensed since 2005 and are recommended for 11-12-year-olds: HPV; MCV4 (the first meningococcal conjugate vaccine); and Tdap (the new tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine) [13].

Earlier doctor-patient-parent discussion in the context of routine vaccinations and preventive health care may have tempered HPV vaccine's association with adolescent sexual activity in general and Alex's sexuality in particular. But Dr. Carson's timing is not unusual. Despite CDC recommendations, physicians are more likely to recommend HPV vaccination for 13-15-year-olds than for 11-12-year-olds [11, 14]. The perceived need to discuss sexuality with patients before offering the HPV vaccine appears to serve as a barrier both to recommendation by physicians and acceptance by parents [11]. This may be an artifact of the introductory phase of this vaccine. Just as with hepatitis B, if HPV vaccine is part of a panel of vaccines offered at the same time, the perceived link to sexuality may decrease.

Alex's mother objects, "The HPV vaccine is mandated here in Virginia for 11-year-old girls. I would have chosen to opt-out of the mandate because I don't want my daughter to act irresponsibly or suffer unknown side effects."

Virginia is one of two jurisdictions (along with Washington, D.C.) to mandate HPV vaccine prior to middle school entry. The mandate, enacted in 2008, did not affect Alex, but, as her mother's statement suggests, the mandate does not obviate the need for parental permission, and the grounds on which parents can opt out of the mandate are generous. All state mandatory vaccination laws allow parents to opt out for legitimate medical reasons, many allow opt-outs on the basis of religious beliefs, and some for philosophical or personal beliefs [15]. The option to decline the HPV vaccination in Virginia is quite broad: parents can refuse the vaccine for any reason after having reviewed materials describing the link between HPV and cervical cancer [16].

Such parental reluctance is not unusual. A national survey of pediatricians and family physicians conducted in 2008, 18 months after HPV vaccine was licensed, found that over half of the physicians surveyed reported that at least one-fourth of parents of 11- to 12-year-old patients refused (defined as "outright refusal without plans for future vaccination") or deferred (defined as "postponing vaccination with the intention of considering it in the future") HPV vaccine. Refusals and deferrals were less frequent for 13- to 15-year olds [11]. While few physicians think that vaccination encourages earlier or riskier sexual behavior, almost half reported that parents were concerned about this.

Even though vaccine safety is a concern shared by physicians and parents, these concerns have lessened with time [4, 11]. Nevertheless, parents still worry that HPV vaccine is not safe enough. By 2008 few physicians reported concerns about HPV vaccine safety, but over one-quarter of surveyed physicians reported that parental worries about safety remained a barrier to vaccine acceptance [11]. The CDC website on vaccine safety includes up-to-date information about the HPV vaccines [17]. As of June 2011, over 35 million doses of Gardasil had been distributed, and postmarketing surveillance data attest that Gardasil remains generally safe and effective. Because adolescents are prone to fainting or orthostasis after injections,

with risk of falls and injury, both the FDA and the CDC recommend lying down for 15 minutes after receiving the vaccine.

Education helps to overcome parents' reluctance to consent to the HPV vaccine, especially education that highlights the reduced risk of cervical cancer after vaccination [11]. Physician recommendation increases immunization acceptance in general and the same is true for HPV vaccine [11, 18]. A recent study shows that a strong physician recommendation of the HPV vaccine results in four times the rate of parental support [19]. One of many toolkits to help educate patients and their parents about the vaccine is available at http://www.hpvvaccineproject.org/hpv.php?page=providers_involved. The American Academy of Pediatrics (AAP) website also has helpful information about ways to respond to various reasons for refusing vaccination, as well as suggestions for documenting the discussion and coding the reason why a vaccine was not administered.

Alex responds angrily. "I'll come back to Dr. Carson's office alone, or get the vaccine at Downtown Family Planning," she says, referring to a Title-X clinic near where they live in Richmond.

As discussed above, the kinds of medical treatment that adolescents can consent to without their parents is determined by state law. In Virginia Dr. Carson is most likely correct in her assessment that she cannot legally give Alex the vaccine without parental consent. While minors in Virginia can consent to medical services "required in case of birth control, pregnancy or family planning," as well as to services that test or treat sexually transmitted or other reportable diseases, the statutes do not explicitly cover *prevention* of sexually transmitted diseases. The law in other states may, although the language in the Virginia statutes is fairly typical. When these statutes were adopted the existence of a vaccine to protect against a sexually transmitted infection was not anticipated, so the fact that the statutes do not contain specific exclusion or inclusion of such preventive measures is not surprising [20]. California recently responded to this omission and passed specific legislation to allow minors to consent to HPV vaccination [21].

If Dr. Carson cannot give Alex the vaccine without parental consent, Alex will not have any better luck receiving the vaccine by coming back to Dr. Carson's office alone. But, what if Alex goes to a nearby family planning clinic supported by federal Title X funds? Such a clinic may provide the vaccine, although that is not guaranteed, as services are not uniform across Title X clinics, and the vaccine is expensive, about $120 per injection for a series of three injections. In addition, while Title X clinics are legally required to safeguard the confidentiality of minors seeking services there, the scope of the services they can provide without parental consent may be limited by the same state laws that apply in Dr. Carson's office. This is an area of the law that is both unclear and evolving [2, 22].

Dr. Carson finds herself in an uncomfortable and unfortunate situation. She should let both Alex and her mother know that she is not able to provide the vaccination without parental consent. It is possible that a strong recommendation by Dr. Carson will persuade Alex's mother to allow Alex to receive the vaccine, if not during this visit, then a later one. Before forcing the issue and taking a strong position in favor of the vaccine, Dr. Carson may need to meet with Alex and her mother separately, and confidentially, followed by a three-way conversation that looks for common ground and promotes trust. Time usually helps. Dr. Carson can provide Alex and her mother some literature on the vaccine and suggest that they give it some more thought and come back to discuss at a return appointment, which would optimally be scheduled before they leave the office.

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CLINICAL CASE
Writing an Excuse or Educating the Patient
Commentary by John J. Frey III, MD

Dr. Sanders is a family physician practicing in a private clinic in Wisconsin. In autumn of 2009, Dr. Sanders was inundated with questions and concerns from patients regarding the H1N1 pandemic, especially since over 2,000 cases had been identified in Wisconsin and neighboring states. In fact, many deaths had been attributed to the virus, mostly in young children, the elderly, and pregnant women. Dr. Sanders and her staff struggled to assuage patients' concerns by providing up-to-date information on the virus and administering the H1N1 vaccine to all high-risk patients. After several weeks, though, the vaccine supply had run low, and some who wanted the vaccine were unable to get it.

One morning on her walk to work Dr. Sanders met two patients, Mrs. Alcott and her 12-year-old daughter Jessica. Mrs. Alcott expressed anxiety about Jessica's safety and asked Dr. Sanders if she could give them both the H1N1 vaccine.

"Unfortunately, our supply of the vaccine has been used up," Dr. Sanders explained, "and we don't have any more to give to even our high-risk patients. Neither does the hospital's emergency department. I'm sorry to say it seems like it may be a week or longer before we get more."

Mrs. Alcott's eyes widened. "A week? And there are so many unvaccinated people. This is too dangerous. We're just going to have to stay home until we can get the shots." She asked Dr. Sanders to write both of them doctor's notes excusing them from work and school for two weeks.

Commentary
Over 35 years ago, Ivan Illich first used the term "social iatrogenesis," which he defined as "designating all impairments to health that are due precisely to those socio-economic transformations which have been made attractive, possible, or necessary by the institutional shape health care has taken" [1]. Social iatrogenesis, in his view, is an historical "contract" that medicine has made with society whereby many problems of life are medicalized in the institutions and in the physician's control, putting doctors in the position of creating a wide variety of clinical and social dependencies.

Most of us who have practiced for any length of time have seen the dramatic increase of forms, permissions, papers, and other required material that serve a patient's needs to interact with the society in which we function. These forms are examples of social

iatrogenesis. Physicians "certify" everything from driver's license restrictions, maternity leaves, and competence to a patient's level of disability, administration of medications to school children, and excuses from a type of work for myriad reasons. When we decided on medicine as a career, we most likely knew little of this societal function of doctors. But our social iatrogenic function—deciding for society on who is "worthy" of what treatment, what excuse, or what diagnosis—is something I would venture to say none of us understood prior to finishing medical school. This function has become a burden to both us and our patients and increasingly feels out of control.

When I practiced in the National Health Service in Wales for a year 30 years ago, I anticipated a paper-free life compared to my work in a community health center in the U.S., and, to a great extent, the experience met my expectations. No bills, no insurance forms, no prior authorization, and so on. But what surprised me was the flood of patients who required nothing more than a work excuse for a common illness. Work slips consume a large proportion of the general practitioner's (GP) work—one study calculated that letting discharging doctors give illness excuses to patients leaving the hospital rather than the current understanding that such excuses could only be written by GPs would reduce GP visits by 518,000 yearly—or free up 42,000 GP work hours [2, 3].

Societies, not doctors, should arrange for conditions to deal with short-term illness without requiring patients to sit for hours in doctors' offices to get a piece of paper. Workers deserve to have sick days without having a doctor's excuse. But the same situation exists in the U.S. today for many people. Many hourly workers in our society need a sick note to miss work while higher-paid white-collar workers can take sick days on their own. For many patients, the threat of losing a job either forces them to work when they should be home recuperating or makes them come to the doctor for a work excuse.

The case of Dr. Sanders and Mrs. Alcott and her daughter shows another perspective on the physician as an agent of society, dealing with the consequences of a failed system of public health and public education. Prevention is commercialized, often promoted by "helpful" commercial entities like pharmacy chains and grocery stores which, as a marketing tool, buy up flu vaccine and give it to all who are willing to pay, regardless of evidence-based public health advice. And, as the case suggests, emergency departments seem to have shown the same lack of priority setting by administering shots to whomever shows up and helping to add to the shortage for those who truly need rather than just want it.

The combination of poor communication to the public by the media and vaccine producers, who often underestimate the necessary number of vaccines doses, created a dilemma for Dr. Sanders.

The "correct" advice to Dr. Sanders's patient is that she and her daughter are low-risk individuals and that efforts should be made to use any available vaccine for

high-risk members of the community. The issue is one both of good public health practice and social justice. However, what Mrs. Alcott sees in the community is a rush on immunizations that she has missed for her family, and she is left to worry, unreasonably, that they might suffer adverse consequences. Dr. Sanders can review the medical priorities and seek to reassure Mrs. Alcott about her and her daughter's risk, explaining that effectively quarantining themselves will not eliminate risk and, depending on the length of time to obtain more vaccine, might last much longer than a couple of weeks.

Dr. Carson's appeal to the patient's request for an excuse is a plea for reasonableness. As Norman Daniels states, requiring "accountability for reasonableness makes it possible to educate all stakeholders about the substance of deliberation about fair decisions under resource constraints. It facilitates social learning about limits. It connects decision making in health care institutions to broader, more fundamental democratic deliberative processes" [4]. Our current society is driven more by individual demands than the collective social good. The response of the "market" to patients as "consumers" who, even if expressing unreasonable demands, need to be served cannot deal in a fair way with problems of rationing of important resources like flu vaccine. If we as a society can't do it with flu vaccine, how will it deal with larger issues such as high cost-technology, screening for disease, or Medicare costs?

Dr. Sanders can work against the flow of the market and patient as consumer, using a scientific approach that emphasizes individual and societal risk. But that may not be enough to dissuade Mrs. Alcott. For the sake of her own integrity, the doctor needs to take that risk. Dr. Sanders could write a note for Mrs. Alcott describing the unavailability of vaccine and the time it may take to obtain some, but not advising Mrs. Alcott and her daughter to stay home. Advocacy for Mrs. Alcott for an irrational position for both her and her daughter would not be appropriate in this instance.

Mrs. Alcott could take the note describing the unavailability of vaccine to her work or her daughter's school and let the job or the school decide what to do. It is consistent with Illich's point about social iatrogenesis that we *not* create "sickness" where there, in fact, are only conflicting beliefs and opinions in a society. Dr. Sanders' position also might be that, as a physician in a community, she has obligations to help move informed policy back to where it should be—in the institutions like workplaces and schools where the public, not individuals, decide who is sick and who is well.

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CLINICAL CASE
Treating Children Whose Parents Refuse to Have Them Vaccinated
Commentary by Kimberly Insel, MD, MPH

Dr. Feyn, a Denver pediatrician, mentions to his colleague Dr. Manning that parents' refusal of vaccines for their children has become more popular among parents in his patient panel in the last 5 years. "Most of these parents have similar reasons for choosing not to vaccinate their children. They cite alternative vaccination schedules, celebrity campaigns against vaccine side effects, even online forum discussions with other parents."

Dr. Manning responds, "The CDC has recommended schedules for vaccination, but I know you would like to respect the discretion of patients and parents of patients as much as possible. So what are you going to do?"

"In the past I have documented the vaccine refusal and moved on, but I'm considering changing my approach," Dr. Feyn responds. "As the number of unvaccinated children in my practice increases, I wonder if I am creating a risky environment for vaccine-preventable infections in my community. We recently witnessed an outbreak of pertussis nearby in Boulder because the percentage of immunized kids at a certain school was below threshold necessary for herd immunity.

"I'm thinking of insisting that my patients receive vaccinations according to the standard schedule, unless, of course, there is a specific health-related reason why an individual child should not be vaccinated. I am also considering not treating children in my practice unless they are vaccinated. What do you think of that?"

Commentary
Parental refusal of vaccination for children has led to an emergence of vaccine-preventable illness nationally. In the case of vaccination against measles, national trends of vaccine refusal have increased the number of measles cases. According the Centers for Disease Control and Prevention's (CDC) *Morbidity and Mortality Weekly Report (MMWR),* between January 1st and May 20th, 2011, 24 states reported 118 cases of measles [1]. This is the highest number of measles cases reported since 1996. Of these cases, 89 percent were unvaccinated persons.

Outbreak investigations over the past 4 years reveal increased numbers of cases related to intentional refusal of vaccination by parents. In an outbreak of measles in San Diego County in 2008, an association was found between cases and intentional avoidance of vaccination [2]. In this instance, one imported case of measles resulted

in 839 exposed persons. Both the index case and 75 percent of all related cases were in children whose parents had intentionally avoided vaccinating their children. Similarly, many of the 21 children affected by the largest measles outbreak in 2011 were unvaccinated because of parental concerns about the safety of the measles, mumps, and rubella (MMR) vaccine [3, 4].

Although the problem of inadequate vaccination is not an entirely new problem, the role of the physician in protecting vulnerable populations cannot be overemphasized. To understand whether it is ethical not to treat children whose parents refuse to vaccinate them, it may be beneficial to define the population of interest and strategies found to be effective in communicating with their parents.

Vulnerable Populations

Particularly vulnerable populations of children are those that cannot be immunized or develop an immune response. These children rely primarily on herd immunity, the vaccination of a critical mass of the population against life-threatening diseases. These populations include children under 12 months of age (too young for vaccination) and children who have chronic medical conditions that prevent them from being able to receive vaccinations. In 2011, 15 percent of cases of measles were in children too young for vaccination. Within the 165 deaths associated with measles cases between 1987 and 1992, 14-16 percent were in children who had pre-existing conditions that prevented them from being vaccinated [4]. Vulnerable groups of children are at particular risk when exposed to the children of parents who willingly choose not to vaccinate their children, not only because of their increased susceptibility but because that increased susceptibility can also lead to worse sequelae in those infected [5].

Other vulnerable populations include children who are not vaccinated for reasons other than medical indications. An analysis of the risk of measles within the population of children exempt from vaccination for nonmedical reasons showed that between 1985 and 1992 these children were 35 times as likely to contract measles as those without exception [6]. Requirements for vaccination of children in school have also waned. As more nonmedical exemptions from vaccination are accepted by schools, cases of vaccine-preventable illness rise [7-9]. Traditionally, it has been the role of public health authorities to protect the most vulnerable groups within a population. If vaccination refusal is leading to more cases of vaccine-preventable illness affecting vulnerable groups of children, it is imperative that we equip physicians and parents with tools to assist in protecting children at risk.

A History of Vaccination Requirements

Vaccination status improved nationwide after 1962 when the Vaccination Assistance Act was passed, providing ongoing financial support to state or local health departments. Initial goals set in 1977 by the Childhood Immunization Initiative were to achieve 90 percent immunization levels. These goals were superseded in 1980 when 50 states passed laws requiring immunizations for students entering schools. With improved vaccination rates nationally, vaccine-preventable deaths decreased.

Vaccine adverse events were recorded as early as 1972 and developed formally into the Vaccine Adverse Events Reporting System in 1986—a passive surveillance system receiving reports nationally from clinicians and the families of vaccine recipients [10].

Trends in Vaccine Refusal

Early surveys of vaccination refusal by the National Immunization Program demonstrated several reasons for vaccination refusal, the most prevalent of which were fear of vaccine safety and the perception that vaccines did not provide sufficient benefits to outweigh the risks [11-14]. Controversy over vaccine safety began to grow in 1980, after some allegations were made that the diphtheria/tetanus/pertussis (DTP) vaccine was a cause of infant deaths and other permanent injury. Following early doubts in vaccine safety, vaccine refusal focused on unsubstantiated claims that vaccines were associated with the onset of autism, attention deficit disorder, and other cognitive deficits affecting children.

Vaccine refusal is thus not a new problem. Cases of vaccine-preventable disease resulting from inadequate vaccination were identified in the 1980s and '90s. At that time, vaccine-preventable illness predominantly affected unvaccinated preschool- and school-aged children [15, 16]. Between 1987 and 1992, it was estimated that there were 165 measles-associated deaths [4], accounting for an attack rate of 2.54-2.83 deaths per 1,000 reported cases in the United States. Deaths related to measles, a vaccine-preventable disease, were most commonly caused by measles-associated pneumonia or encephalitis. These deaths occurred out of a total of over 55,000 cases of measles in the United States during the same period [4].

The vaccination refusal that physicians see varies by community and specialty, but some surveys have found trends. One survey found that parents of unvaccinated children were more likely than parents of undervaccinated children (those who receive at least one vaccine) to be white, married, college-educated, and high-income earners and to have five or more children [17]. Another study found that the parents of unvaccinated children were more likely than the parents of vaccinated children to have the perceptions that their children were not as susceptible as other children to disease, that the diseases vaccines protected against did not have severe health consequences, and that vaccines were not efficacious in disease prevention [18]. For all parents refusing vaccination, the most common worry regarded vaccine safety.

The Physician's Role

When there is poor vaccine acceptance, the role of the physician becomes crucial. The importance of physicians' role in vaccine acceptance and vaccine-related education cannot be overemphasized. This was demonstrated in the case of a measles outbreak in San Diego. During this outbreak, inadequate vaccination against measles was associated with physicians' assumptions that vaccination was contraindicated in sick children, clinicians' choosing not to give multiple vaccinations in one visit, and private doctors' referring children who lacked insurance to other clinicians [19].

Several studies have found that parents' preferred source of vaccination information is health care professionals [20, 21]. A survey of 21,420 households conducted by the National Center for Immunization and Respiratory Diseases in 2009 concluded that the most important source of help in decisions about vaccinating young children was the child's doctor or nurse. In the survey, 86.5 percent of respondents reported that they usually followed the clinician's advice, and 84 percent reported that they trusted it. A second study from the University of Michigan reiterated the importance of physician advice to parental decision making about vaccination. Of the 2,521 online survey responses, 76 percent of parents reported trusting a physician in regards to vaccine-safety information, and only 2 percent reported not trusting a physician at all [22].

In the context of these data, some strategies may be better than others in approaching parents who refuse vaccination. In light of evidence regarding physicians as trusted sources of information about vaccine safety, it would seem a bit premature to turn away patients whose parents refuse vaccination. Instead, it may be more beneficial to engage the parents of our patients. In this way, we can fulfill our role as patient educators, patient advocates, and public health practitioners. Important to an understanding of our role is a clear acknowledgement of the risk vaccine refusal presents to intentionally unvaccinated children and children who cannot be vaccinated due to age or medical condition. Considering the hundreds of unnecessary deaths and illnesses among children caused by vaccine-preventable illness every year in our country, it is our duty to do what we can to ward off preventable illness. In the case of vaccine refusal, this may take the form of a simple conversation with parents.

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MEDICAL EDUCATION

Residents' Role in Immunizing Adults: Rationale, Opportunity, Obstacles, and Strategies

Jay A. Jacobson, MD

Rationale

Childhood vaccination is one of the greatest and most dramatic successes of modern medicine and is responsible for reduced incidence and even the disappearance of previously common and serious childhood diseases. Compared to childhood vaccination, however, adult vaccination has not been as successful, and more adults die each year from vaccine-preventable diseases [1]. An embarrassingly high number of adults become ill, are hospitalized and even die because of infections that physicians can but don't prevent.

Medical residents are certainly not solely responsible for this disturbing problem, but they can help solve it during their training and later in their practice. Residents care for a high proportion of patients who are particularly vulnerable to preventable infections because of age-related declining immunity, chronic illnesses, or immunosuppressive treatments. Our medical care system has not done a good job of identifying and vaccinating at-risk adults.

Although immunization is one of the most effective public health measures to prevent disease, vaccination rates in adults remain low [2]. As recently as 4 years ago, about 64 percent of adults over 65 and 31 percent of adults 18-64 were vaccinated against influenza. The influenza vaccine is now recommended for all adults regardless of underlying risk factors. As for other vaccines, 57 percent of adults have been vaccinated for pneumonia and 44 percent for tetanus/diphtheria toxoid. Thirteen percent of men who have sex with men have been vaccinated against hepatitis B [3].

Two vaccine-preventable diseases, influenza and pneumococcal pneumonia, the most common cause of community-acquired pneumonia (CAP), provide dramatic evidence of the problem and potential progress we can make. In 2005, more than 60,000 adults died of pneumonia in the United States, where it is the eighth leading cause of death. Hospitalized patients with pneumonia required an average stay of more than 5 days, 20 percent were admitted to an intensive care unit, their mortality rate was as high as 23 percent, and the economic burden of CAP is more than $17 billion annually [4]. Residents cared for many of these individuals during their admission for pneumonia, but they or other residents likely encountered these same patients earlier for other reasons in their clinics, the emergency room, or in the hospital.

The Centers for Disease Control and Prevention (CDC) estimates that for every one million vaccinated people older than 65 years, about 1,300 hospitalizations and 900 deaths can be avoided in a typical season [3]. Similarly, herpes zoster (shingles) affects one in three people during their lifetimes, causing about one million cases per year in the U.S., mostly in adults over 60 or with immune-compromising conditions. A still-underused but safe and effective zoster vaccine was introduced in 2006 [5].

Because some infections are both preventable and communicable, a resident who immunizes her patient against influenza or hepatitis A or B, for example, may not only prevent illness in that patient, but also in a spouse, children, or other contacts. Furthermore, even in the particular immunized patient, the benefits may multiply. In individuals over 65 with cardiovascular disease, influenza vaccination has resulted in a 60 percent reduction in death from all causes, including myocardial infarction, cerebrovascular accident, and congestive heart failure [6].

Opportunities

Clinic visits. A clinic visit with a patient has some characteristics that create an excellent opportunity to review immunization status and risk factors for particular infections and to actually administer vaccines. The patient is not as likely to be as seriously ill as an inpatient and is therefore more able to provide relevant history and information and to understand, respond to, and comply with a suggestion to be immunized. The resident is more likely to have a prior relationship with a clinic patient and to see him or her again. This should help establish trust, which may be critical in the decision to be immunized. It may also strengthen the resident's sense of obligation to the patient and the patient's future health. No resident wants to hear that her clinic patient has gotten sick or died from an infection that she could have prevented.

An immunization during a clinic visit scheduled for another reason is efficient and more likely to be accepted by patients than a visit scheduled exclusively for a vaccination. The clinic chart may be a better resource for immunization history and a better place to document vaccinations than the inpatient record.

Spouses or other family members often accompany patients to the clinic. It's not unreasonable to inquire about their immunization status as well. If they, too, would benefit from a vaccine, the clinic is generally well suited to provide it for them. Here is another chance to reap a dual benefit. If the patient has an impaired response to a vaccine, a fully immunized contact may be less likely to acquire infection from or transmit infection to the patient.

Hospitalized patients. Inpatient admissions, while perhaps not ideal times to discuss and provide prevention for future infections, are opportunities to do so and may even have some advantages. Certainly, for some patients, a hospitalization is their first or only contact with the health care system. For these patients and those with intermittent visits and no primary care physician, a hospital stay may provide the best or only opportunity to immunize them [7]. For these patients and virtually all

others, the prospect of being seriously ill and returning to the hospital is not an appealing one, hence they may welcome a chance to prevent the infection that could cause such an event. If a vaccine is indicated for an inpatient based on risk factors or guidelines, then giving it during admission is more reasonable and efficient than scheduling an outpatient visit exclusively for that.

The relationship that a resident builds with a hospitalized patient can also serve as the basis for trust that makes vaccine acceptance more likely. The fact that the resident shows concern for the patient's future health can enhance the patient's regard for the doctor and perhaps even improve adherence to other recommendations. Many respected professional and public health organizations, including The Advisory Committee on Immunization Practices, the Centers for Medicare and Medicaid Service, the American Thoracic Society, and the Infectious Diseases Society of America [6], have endorsed immunizing hospitalized adults against influenza and pneumococcal disease. *The emergency department*. An emergency room visit seems an unlikely setting in which to consider immunization, but there are some paradoxical situations and some reasonable imperatives that arise there. When, in early fall, a 55-year-old man comes to the ER with a cough and fever and has a radiograph with a lobar infiltrate, most residents would recognize community-acquired pneumonia and treat it appropriately. Some residents would recognize that this was a preventable infection and that it, by itself, may not prevent future similar infections. It might actually indicate that the patient is at increased risk of those infections. These residents might consider and recommend pneumococcal or influenza vaccine or both for such a patient and, depending on the treatment plan, actually give the vaccines in the ER or recommend they be given in the hospital or at a follow-up appointment.

The most common trigger for immunization in the ER is an injury or laceration. That often prompts a question about relevant immunization history followed by a shot of tetanus or tetanus and diphtheria toxoid. The National Hospital Ambulatory Care Survey from 1992 to 2000 showed that ERs gave 27,738,800 vaccines, 93 percent of which were for tetanus [6]. Specific exposures also lead residents and attending physicians in the ER to commonly give rabies or hepatitis vaccines. Because those who seek care in the ER are more likely to be underimmunized, less likely to receive regular physician care, and more likely to be of lower socioeconomic status than patient who do not come into emergency departments, the ER provides a good—and often the only—opportunity for prevention. That may be particularly true for influenza and pneumococcal immunization, but the opportunity is rarely used [6].

In one study of patients with risk factors who developed pneumococcal bacteremia, nearly 90 percent had been in an ER during the preceding 5 years. Only about half had been a medicine inpatient and only about a third had been in a general medical clinic [6]. Thus, from a risk-benefit perspective, the ER may actually be the best opportunity to immunize against that infection, but certainly not the only setting in which to do so. The Centers for Disease Control, Advisory Committee on

Immunization Practices, and the American College of Emergency Physicians support immunization of ER patients against pneumococcal pneumonia and influenza [6].

Obstacles and Objections

Pediatric residents devote considerable time and attention to immunization of their young patients. They appropriately consider vaccines a routine but also significant action they can take to protect their predominantly healthy patients. Medicine residents more often strive to maintain the health of patients with chronic illness, manage complications, and diagnose new and potentially serious complaints. For them, job satisfaction and peer approval often come when they successfully manage a difficult problem or correctly deduce an unusual diagnosis from a puzzling set of symptoms and laboratory results. Preventive measures seem less important, get less positive feedback, and are often overlooked in favor of crisis intervention and disease management, especially on a busy day with time for little else. Lack of continuity and sustained relationships dictated by resident schedules also works against a focus on the patient's future as compared with present health.

Because immunizations are not so routine, highly valued, or closely monitored in adult care settings, medical residents don't generally assign them high priority. Adult patients are less exposed to recommendations for vaccines and have less peer dialogue about them than mothers, especially new mothers, who focus intently on the present and future health of their babies. Hence adults, especially older adults with already existing health problems, generally request immunization less frequently. Residents can address this by making sure that clearly written information about immunization is provided to patients and their families during inpatient and outpatient encounters.

Many children and adults face financial obstacles to receiving preventive care, especially if they are uninsured, and many insured adults balk at high copayments. Uninsured adults often have more urgent competing medical expenses. Insurance and Medicare cover most, but not all, adult immunizations. Herpes zoster and travel-related immunizations are among those excluded. Lack of access to vaccines—whether due to distance, difficulty travelling, or receiving most care from a specialist who doesn't provide immunizations—is another obstacle for older and disabled adults.

Specific age-related schedules and legal requirements for school entry create a sense of urgency for childhood immunizations. For adults, injuries prompt use of tetanus toxoid, and the seasonal variation in influenza virus warrants annual fall vaccinations, but vaccines like pneumococcal polysaccharide and varicella do not seem as time-sensitive, are never mandatory, and may be subject to procrastination by both patients and physicians.

Finally, ignorance and misperceptions about vaccine-preventable diseases and vaccines themselves reduce desire for vaccination and lead to objections to their use. Patients, who don't realize that they are at risk of shingles or are unaware of

preventive methods, are unlikely to ask for the vaccine. Similarly, persons who know they are at risk of influenza but believe that the risk is low or that the disease is not serious are not likely to request immunization. The beliefs that coincidental symptoms experienced after an influenza vaccination were caused by it, that the flu vaccine is unsafe or ineffective, or that the vaccine actually causes the flu are all powerful barriers to seeking vaccination or accepting it, even when it is recommended by a well-informed and well-intended resident [8].

Strategies

Medicine residents are not responsible for most of the problems with adult immunization and they certainly are not able to eliminate them alone, but they could be a significant part of the solution and provide substantial, safe, effective health benefits to many of their patients. Residents should inform themselves and their patients about the risks, benefits, indications, and contraindications for adult immunizations. They should be prepared with facts to address patient objections and misunderstandings [9].

Vaccine information statements are good sources for the public and professionals. They are available in many languages, which may overcome another barrier, from the Centers for Disease Control. These statements should be available on wards and in clinics and ERs [3]. For patients who refuse influenza vaccine because they believe they have an allergy to eggs or the vaccine, careful questioning may help decide whether there is a contraindication or a need for one of the alternate vaccines now available [10, 11].

Residents should seek and record immunization information in easily retrievable and readily available medical immunization records, preferably electronic ones. If these don't exist in a training environment, residents should advocate for them. Similarly they should encourage systematic prompts for immunization status and vaccine administration. This could include computer algorithms, standing orders, or inclusion in standard questions that nurses ask [12-15]. In the absence of such system tools, residents should give special and added attention to those patients at greatest risk for preventable infections by virtue of their age or underlying chronic disease, immune system suppression, or international travel plans [16, 17].

Residents should be aware of the cost of immunizations provided in their hospitals and, if that is a concern or obstacle for patients, enlist the aid of a social worker to discover what insurance will cover and identify possible alternate payment programs.

Residents should recognize that hospital admission, clinic appointments, and even ER visits constitute opportunities—often the only opportunities—to check immunization status and provide needed and indicated vaccines [6, 7]. They can take advantage of these encounters and make them more efficient by including preventive measures in an otherwise diagnostic or therapeutic visit. Two vaccines frequently given as a pair, known to be safe and effective, are those for pneumococcal pneumonia and influenza [3].

If immunization is impractical or impossible in the hospital at a particular time, such as flu vaccination in August, residents should encourage patients to take advantage of convenient, timely immunizations now often available at grocery and "big box" retailers.

While it may not affect adult immunization directly, residents who choose to have themselves immunized against vaccine preventable diseases, hepatitis B and influenza in particular, benefit patients by reducing their exposure while they are in the hospital and quite vulnerable. These residents also serve their colleagues by being less likely to miss work during the normally very busy flu season. They are role models for patients and more convincing advocates for vaccination.

Current Adult Immunization Recommendations

Residents should consult the cited article in the CDC's *Morbidity and Mortality Weekly Report* or the CDC.gov web site for more details, but the basic recommendations are summarized below.

The Advisory Committee on Immunization Practices (ACIP) recommends that all adults, regardless of risk factors, receive influenza and tetanus immunization. Because of frequent changes in the influenza virus, one dose of influenza vaccine should be given every year. Adults, nearly all of whom were vaccinated against tetanus as children, need only receive a booster injection every 10 years with the tetanus diphtheria (Td) vaccine. For their first booster the tetanus, diphtheria, pertussis (Tdap) vaccine provides additional protection against pertussis. The ACIP recommends other vaccines for adults based on their age and underlying health conditions. Adults at least 60 years old should receive one dose of zoster vaccine. Younger adults with chronic medical conditions and organ failure should also receive it unless they have immunocompromising conditions. One or 2 doses of pneumococcal vaccine should be given to adults with diabetes, organ failure, alcoholism, or asplenia and those who smoke or live in long-term care facilities. Recommendations for varicella, human papillomavirus, measles, mumps, rubella, meningococcal, hepatitis A, and hepatitis B vaccines are based on age, prior immunity, and the presence of particular underlying conditions [18, 19].

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THE CODE SAYS
The American Medical Association *Code of Medical Ethics*' Opinion on Physicians' Responsibility to be Vaccinated

Opinion 9.133 Routine Universal Immunization of Physicians
As professionals committed to promoting the welfare of individual patients and the health of the public and to safeguarding their own and their colleagues' well-being, physicians have an ethical responsibility to take appropriate measures to prevent the spread of infectious disease in health care settings. Conscientious participation in routine infection control practices, such as hand washing and respiratory precautions is a basic expectation of the profession. In some situations, however, routine infection control is not sufficient to protect the interests of patients, the public, and fellow health care workers.

In the context of a highly transmissible disease that poses significant medical risk for vulnerable patients or colleagues, or threatens the availability of the health care workforce, particularly a disease that has potential to become epidemic or pandemic, and for which there is an available, safe, and effective vaccine, physicians have an obligation to:
(a) Accept immunization absent a recognized medical, religious, or philosophic reason to not be immunized.
(b) Accept a decision of the medical staff leadership or health care institution, or other appropriate authority to adjust practice activities if not immunized (e.g., wear masks or refrain from direct patient care). It may be appropriate in some circumstances to inform patients about immunization status.

Issued June 2011 based on the report "Routine Universal Immunization of Physicians for Vaccine-Preventable Disease," adopted November 2010.

Related in VM
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HEALTH LAW

The National Childhood Vaccine Injury Act and the Supreme Court's Interpretation

Valarie Blake, JD, MA

Vaccine immunization has been at the center of a number of legal and ethical controversies, particularly over the last several years, with mandated vaccines for military workers and concerns about links to autism dominating the media coverage. In February 2011 the U.S. Supreme Court weighed in on a particularly important issue related to the safety of vaccines and recovery for injuries caused by them. *Bruesewitz v. Wyeth* wrestles with the tension between ensuring that companies can afford to produce vaccines, which are good for the many, and protecting and compensating the few who suffer from vaccine-related injuries [1]. The ruling on *Bruesewitz* shields vaccine manufacturers from certain legal liabilities—protections the Court believed were set forth in the National Childhood Vaccine Injury Act. Because it touches on safety, liability, and public interest, the case will certainly play an important role in future suits related to vaccines but also, potentially, other public health measures.

The National Childhood Vaccine Injury Act

The twentieth century saw the introduction of widespread vaccination and, consequently, the elimination of a number of communicable diseases, particularly in children [2]. Championing the success of vaccines, all 50 states have instituted laws requiring at least some vaccines as a condition of a child's being enrolled in school [3]. In the 1970s and 1980s, however, as many communicable diseases were eradicated by vaccine, the public began to focus on the injuries caused by vaccines, leading to an increase in vaccine-related litigation. The total number of liability suits against vaccine makers rose from nine between 1978 and 1981 to more than 200 suits per year by the mid-1980s [4].

Fearing that this increased liability would drive vaccine manufacturers out of the market, Congress intervened in 1986 with the National Childhood Vaccine Injury Act (NCVIA) [5]. The act establishes a special court program for vaccine injury claims that caps damages and allows for the injured party to be compensated without having to prove that the maker committed any wrongdoing. Recognizing that even the best vaccines may harm some individuals but still serve the broader public, the court system is designed to limit liability for manufacturers (thus encouraging them to remain in the vaccine-making market), while ensuring that injured persons have a speedy and cost-effective mechanism for receiving compensation.

NCVIA establishes a Vaccine Injury Table of all possible types of vaccines, associated side effects, and timelines for experiencing side effects that may warrant compensation. If someone has suffered an injury that fits the criteria listed on the table, he or she does not need to prove that the vaccine caused the injury or that the vaccine was defective in some way [5]. Instead, the burden is on the government to prove otherwise [6, 7]. If the injury is not on the table, the injured person must prove that the vaccine caused the injury, as in a regular tort lawsuit. In either event, if the injured party wins, he or she can be reimbursed for medical care, rehabilitation, counseling, and vocational training expenses, diminished earning capacity, pain, and suffering. Surviving family members receive $250,000 if the vaccine resulted in death. If the case is not frivolous (meaning it has some serious purpose or value), all attorney fees are provided through the vaccine fund [8]. If the injured party does not wish to accept the judgment of the vaccine court, he or she can reject it and seek relief through the regular court system [7].

Damages are paid from a fund raised by taxes on vaccines, and manufacturers are generally shielded from liability so long as they comply with certain regulatory requirements and do not commit fraud, engage in criminal or illegal activity, or intentionally withhold information from the patient [9]. Manufacturers are not liable for any "unavoidable, adverse side effects," the interpretation of which was the focus of the *Bruesewitz* case [9].

Bruesewitz v. Wyeth

In 1992, newborn Hannah Bruesewitz received a diphtheria, pertussis, and tetanus (DPT) vaccine from her pediatrician, in accordance with the vaccine schedule set forth by the Centers for Disease Control at the time [9]. The vaccine had been approved by the federal government in 1948, 1953, and 1970. Within 24 hours of injection, Hannah began experiencing seizures, more than 100 occurring in the first month alone. When Hannah reached her teens, she continued to suffer from seizure disorder and developmental delay [9].

Hannah's parents' first claim in the vaccine court in 1995 seeking recovery for their daughter's injuries was unsuccessful because her injuries were not listed on the vaccine injury table [1, 10]. Mr. and Mrs. Bruesewitz then sued the manufacturer, Wyeth, outside of vaccine court. They lost, appealed, and lost again before the Supreme Court agreed to review the case.

Hannah's parents argued that Wyeth was responsible for Hannah's injuries because the vaccine was defectively designed by the manufacturer. The majority of the court concluded that a defective design claim is barred by the National Childhood Vaccine Injury Act and, thus, Wyeth was not liable for the injuries caused to Hannah. They interpreted the NCVIA to mean that all side effects, including design defects, are not subject to liability claims so long as "there was proper manufacture and warning" [11]. While lawsuits against other types of product manufacturers generally allow an injured party to sue for any of three problems (defective manufacture, inadequate

warning, and defective design), the Supreme Court read the act as insulating vaccine manufacturers from the third claim (defective design).

Although the majority of the Supreme Court agreed with this opinion, two justices wrote a dissent that questioned the court's interpretation of the National Childhood Vaccine Injury Act. These justices argued that the majority's view removed a previously existing legal duty of vaccine manufacturers "to improve the designs of their vaccines in light of advances in science and technology." Examining the legislative history and text of the statute, these justices believed that vaccine makers should be exempt from liability only if the vaccine was properly manufactured and labeled and if the side effects of the vaccine "could not have been prevented by a feasible alternative design" that did not "comprom[ise] the vaccine's cost and utility." The majority discounted this view, arguing that Food and Drug Administration (FDA) regulations still applied to regulate the safe manufacturing of vaccines.

Wider Implications of the Ruling

The ruling in *Bruesewitz* has some important implications for future vaccine cases and public health interventions more generally. Note that the *Bruesewitz* decision was not calling into question whether a no-fault type of court was appropriate for public health interventions, like vaccines. Instead, the judges were debating what grounds still remained for a person injured by a vaccine to be compensated. The majority's holding will certainly make additional legal cases against these companies more challenging, as vaccine manufacturers are now not liable for failing to improve vaccine designs and defects, unlike manufacturers of other products.

If applied broadly, the Supreme Court's holding could also draw important new standards for public health interventions. The scope of the *Bruesewitz* case is limited in that it applies a specific statutory requirement for vaccines only. However, to the extent that the Supreme Court prioritized the need to promote public health (and thus financial incentives for health care goods manufacturers) over the need to protect individual health when it insulated health care products manufacturers from liability to update and modernize their technology, this holding could have far-reaching implications for other public health interventions and legal claims in the future.

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POLICY FORUM

Should Participation in Vaccine Clinical Trials be Mandated?

Susanne Sheehy, BM BCh, MRCP, DTM&H, and Joel Meyer, BM BCh, MRCP

Few would argue with Bill Gates when he describes vaccination as "the most effective and cost effective health tool ever invented" [1]. To date vaccination has saved many lives and has the potential to save millions more, especially if vaccines are developed against the "big three": malaria, HIV, and TB [2-5]. Vaccine development, however, comes at a price that is not only financial but societal. The lack of animal models that can reliably predict vaccine efficacy means that development still unavoidably relies on testing of novel vaccines in healthy individuals. Given the often unquantifiable risks to the recipients of vaccines in early stages of development, clinical trials have traditionally relied on informed and consenting volunteers who appreciate the potential risks but still choose to participate for altruistic reasons [6, 7]. But relying on altruism alone to facilitate clinical trials is potentially unsustainable and ethically contentious.

In recent decades there has been a distressing decline in the numbers of healthy volunteers who participate in clinical trials [7], a decline that has the potential to become a key rate-limiting factor in vaccine development. Reasons for this decline are unclear but are likely to be multifaceted. One familiar problem is the payment of volunteers [8]. To date, the relatively meagre compensation that participants often receive could be seen to belittle and undervalue the contribution of these individuals to global health. The modest financial remuneration commonly provided often means that students and the unemployed make up the bulk of volunteers [6, 8, 9]. As a result, the risks of developing a health intervention that would benefit the whole population are carried disproportionately by some of society's most poor and vulnerable. This is a situation few would judge to be fair or ethical. However it is hard to increase volunteer payment without creating financial incentives. "Danger money" is frowned upon as an inducement that inevitably clouds an individual's appreciation of risk, limiting the likelihood that consent is informed [6, 7]. As a result, consensus has generally dictated that payment for volunteers' trial involvement be modest and limited to compensation for travel, time, and inconvenience only.

If progression of promising vaccines from the lab to the clinic is to remain unaffected and financial inducement is an ethically unacceptable solution to the recruitment shortage, other strategies need to be considered. Compulsory involvement in vaccine studies is one alternative solution that is not as outlandish as it might seem on first consideration. Many societies already mandate that citizens undertake activities for the good of society; in several European countries

registration for organ-donation has switched from "opt-in" (the current U.S. system) to "opt-out" systems (in which those who do not specifically register as nondonors are presumed to consent to donation) [10], and most societies expect citizens to undertake jury service when called upon. In these examples, the risks or inconvenience to an individual are usually limited and minor. Mandatory involvement in vaccine trials is therefore perhaps more akin to military conscription, a policy operating today in 66 countries. In both conscription and obligatory trial participation, individuals have little or no choice regarding involvement and face inherent risks over which they have no control, all for the greater good of society.

As ever, then, the debate boils down to a consideration of the "greater good" or the "lesser evil." A key consideration is the risk benefit ratio—risk to the individual volunteer balanced against the benefit to society. Society is unlikely to accept compulsory recruitment to a trial for a vaccine against the common cold if the vaccine causes severe complications in vaccinees. Increase the severity of the disease in question, however, and compulsory recruitment becomes a more palatable option.

In 2009, initial speculation regarding the H1N1 "swine flu" pandemic set mortality estimates high. In Mexico where the outbreak started, authorities closed public and private facilities [11], putting the interests of society above those of the individual. Although millions of people were infected worldwide, mortality rates were quickly revised downwards [12], and a successful vaccine mass-produced [13]. But consider if this had not been the case. Consider an infectious disease with a high transmission and mortality rate for which vaccine development were possible but limited by a shortage of volunteers willing to participate in clinical trials. Would mandatory participation in clinical trials then be an acceptable policy?

The fundamental principles of medical ethics—beneficence, nonmaleficence, respect for autonomy, and justice—are, as always, conflicted on this issue. Given the inherent risks and common lack of efficacy in many candidate vaccines in development, the principles of nonmaleficence and beneficence would argue against the involvement of subjects in most clinical trials. Justice would reason for the fair treatment of all, supporting mandatory enrollment to help ensure that the risks of developing an intervention that could benefit all are equally borne by all.

Respect for autonomy, on the other hand, would recognize and maintain the right of individuals to self-determination and their corresponding right to refuse a medical intervention. The Universal Declaration of Human Rights upholds the rights, dignity, and freedom of individuals and the need to protect people from "arbitrary interference" [14]—principles that would inevitably be compromised by mandatory enrollment in vaccine trials. Health services depend absolutely on the public's confidence and trust—compromising on respect for autonomy would undermine this fundamental premise and launch us on a precarious slippery slope that may be difficult to climb back up.

A more palatable and realistic option is a policy of "mandated choice." In this case individuals would be required by law to state in advance their willingness to participate in vaccine trials [15]. The advantage of this system is that it could identify a large cohort of willing volunteers from which participants could be recruited rapidly without jeopardizing individual autonomy. It would encourage an open, noncoercive philosophy for tackling societal challenges without compromising individual freedom or public trust in the health care system.

But perhaps most importantly, as a society we need to evaluate our perception of vaccination. Any successful vaccine program by its very nature takes a once-feared illness out of the public eye. This means that the benefits of immunization become forgotten while side effects in small numbers of individuals fill the headlines. It is all too easy for sensationalist and unfounded stories such as that claiming a link between the MMR (measles-mumps-rubella) vaccine and autism [16] to instead take root in society's collective psyche. Ultimately such a crucial public health intervention as vaccine development may become devalued—and only revalued once a drop in vaccination rates leads to resurgence of severe disease.

Perhaps lessons can also be learned from organ donation, where apathy and ignorance may be as much to blame for low donation rates as conscientious objection. If a concerted effort were made to increase public awareness of the success of vaccination, the potential of novel vaccines to improve global health drastically, and the important contribution that individuals can make by volunteering for studies, perhaps mandatory enrollment would not even need to be considered.

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MEDICINE AND SOCIETY

The HPV Vaccine Controversy

Karlie A. Intlekofer, PhD, Michael J. Cunningham, MS, and Arthur L. Caplan, PhD

The development of the human papillomavirus (HPV) vaccine provides an opportunity to prevent the majority of HPV infections that cause genital warts and cervical cancer. Although the vaccine is largely recognized as a medical breakthrough, its acceptance by the public is lagging for several reasons. Contributing factors include underestimation of HPV risk, the challenge of completing a three-shot regimen, concerns about cost, and parental barriers to acceptance. There is also some public concern about vaccine safety in general, although HPV vaccines have excellent safety records. Attempts to publicize the vaccine's safety have been undermined by recent erroneous claims linking the vaccine to mental retardation by political figure Michele Bachmann. These inflammatory and irresponsible remarks mislead the public about the safety and efficacy of the vaccine. We examine the facts concerning the HPV vaccine, its utility, and appropriate responses medical professionals can make to false claims.

Introduction

Among the most recent controversial vaccines are those developed to target HPV, a large category of at least 120 double-stranded DNA viruses. HPV is primarily known for causing *Condyloma acuminata* (genital warts) and is the most common sexually transmitted infection in the Unites States and worldwide [1, 2] The prevalence of genital HPV infection is more than 10 percent among 15-49-year-olds in the United States [3]; however, most infections are cleared within 1 year [4, 5]. Although clearance yields natural immunity, individuals remain susceptible to other strains, and more than 40 of the 120 catalogued HPV types are implicated in the development of genital warts [6]. Approximately 90 percent of genital warts infections are caused by HPV types 6 and 11 [6-8].

More than 20 HPV types cause genital warts and also cause cervical intraepithelial neoplasia, a condition of abnormal growth that can progress to cervical cancer [9]. These high-oncogenic-risk types cause virtually all cervical cancers and most anal cancers [10], and some vulvar [11, 12], vaginal [13], and head and neck cancers [14]. Compared to the clearance rates of types 6 and 11, the oncogenic HPV types show delayed clearance [15-18], and together, oncogenic types 16 and 18 account for more than 70 percent of cervical cancers [19, 20]. Given the role of types 6 and 11 in genital warts and types 16 and 18 in cervical cancer, vaccination against these specific HPV types has been recommended [21] and in a few instances mandated [22].

Vaccine Safety

Cervical cancer ranks as the second most common cancer and the fifth leading cause of death of women worldwide [23]. In response to this serious health issue, more than 20 years of incremental research culminated in the development of HPV vaccines that elicit strong immunogenic reactions without the risk of causing infection [24-26]. Researchers achieved this through the recombinant expression of an HPV capsid protein that spontaneously self-assembles into virus-like particles [27]. These particles form into capsomeres that resemble HPV virions [28] but lack viral DNA; the capsomeres are combined with an adjuvant to elicit robust antibody responses, creating long-term immunity [27, 29, 30].

Vaccines are administered via three intramuscular injections spaced over 6 months. Results of several clinical trials show that vaccinated women remain free of HPV types targeted by the vaccine through the entire duration of the trial [25, 31, 32]. Importantly, the vaccine affords a high degree of protection against HPV infection that extends to protection from associated cervical lesions [33]. Ongoing studies are assessing the duration of protection.

Based on these findings, the FDA approved Gardasil, a quadrivalent vaccine against HPV types 6, 11, 16, and 18 licensed by Merck, in 2006 and Cervarix, a bivalent vaccine for types 16 and 18 made by GlaxoSmithKline, in 2009. Both have been approved and are in use in many nations [34, 35] In fact, the FDA reports that more than 65 million doses of Gardasil have been distributed worldwide [36].

Both HPV vaccines have strong safety records. The most commonly reported adverse events are pain and swelling at injection site [37, 38]. There has been no evidence that Gardasil or Cervarix administration increases rates of death, blood clots, or cognitive impairment. Even though these vaccines continue to generate excellent safety records, low coverage rates in the United States still leave many susceptible to the threat of cervical cancer and genital warts [39].

Maximizing Vaccine Efficacy

HPV vaccination only protects against HPV types to which the individual has never been exposed. Routes of exposure include skin-to-skin and sexual contact [40-42]. It follows that vaccination efficacy is maximized in individuals who are not yet sexually active and thus likely to be HPV-negative. Indeed, clinical studies fail to demonstrate any benefit to women previously exposed to HPV types covered by the vaccine [31, 43]. Acknowledging these facts, the FDA approved Gardasil and Cervarix for females aged 9-26 and 10-25, respectively, and the general consensus among health organizations in the United States and worldwide is for vaccination of girls aged 11-12 [21, 41-47].

Although most research addresses the vaccination impact on female health outcomes, optimizing HPV vaccine efficacy also requires immunizing males. The value of including both sexes in HPV vaccination programs is indirect, in reducing transmission rates to females [48], and direct through the individual protective

effects afforded by HPV vaccination. Males deserve access to a vaccine that can prevent the majority of cases of genital warts, especially considering that males often suffer longer duration of genital warts and incur greater treatment costs than females [49]. Furthermore, HPV is responsible for a wide range of cancers including 70-100 percent of penile intraepithelial neoplasia and 40-50 percent of all invasive penile cancers [50]. In recognition of these factors, the FDA approved Gardasil for the prevention of genital warts [51], anal cancer, and associated precancerous lesions in males in 2010 [36], The prophylactic prevention of HPV infection is clearly warranted regardless of sex, and the vaccination of males is regarded as a cost-effective approach to reduce rates of HPV infection [52].

Finally, research indicates that nonsexual modes of HPV transmission include perinatal transmission from an infected mother [53]. Vertical transmission of the virus occurs primarily during vaginal delivery [54], but HPV can also infect infants delivered by caesarean section [55] and can be transmitted transplacentally to the fetus [56]. Newborns who acquire genital HPV infection may incur higher risks for genital dysplasia and cancer in addition to genital warts. The virus is just as likely to infect the oral mucosa of the newborn as the genitals [57], posing an additional risk of respiratory tract papillomas, which are the most common benign tumors of the larynx in infants and children [58]. Given the diverse manifestations of HPV infection, widespread vaccination coverage holds the potential to benefit a broad range of people.

Sexual Politics and Corporate Suspicions

Although the medical and scientific establishment has embraced the vaccine [59], HPV vaccination rates are inadequate in the United States [39]. Vaccine coverage is hindered by public perceptions regarding HPV's status as a sexually transmitted infection and dissent over the recommended age of vaccination [60]. Social conservatives have countered vaccine mandates with the argument that they infringe upon parental rights to discuss the topic of sex on their own terms [61]. Pro-abstinence activists raise similar concerns that HPV vaccination may increase teenage promiscuity [62], though there is no evidence for this claim [63]. Another suspicion is that HPV vaccine manufacturers have obtained FDA approval through corporate influence in lieu of proper safety testing [64-66]. Finally, several studies have shown that parents fail to vaccinate due to misperceptions about the risk of HPV infection [47].

Inflammatory False Claims

On September 12th, 2011, controversy over the HPV vaccine was reignited by the remarks of Republican presidential candidate Michele Bachmann during a debate. After denouncing an opponent's role in mandating HPV vaccination in Texas, Bachmann made unsubstantiated claims that the HPV vaccine was hazardous. During an interview with Fox News she told this anecdote:

> There's a woman who came up crying to me tonight after the debate. She said her daughter was given that vaccine. She told me her

> daughter suffered mental retardation as a result of that vaccine. There are very dangerous consequences [67].

Bachmann repeated this dramatic encounter during an interview on NBC's *Today* show [68]. These remarks were met with outrage by members of the scientific community, with multiple health and medical organizations denouncing their validity within days [69-71]. In jockeying for political gain, Bachmann disseminated false information to the detriment of public health. She made no attempt to apologize for her remarks or correct them. In fact, she reasserted her claims about the danger of the vaccine as recently as November 2011 [72]. As a public figure with access to an enormous audience, her promoting misconceptions that lead to higher risk for women, men, and babies is inexcusable.

Such events are likely to increase public distrust of vaccines and confusion, but the ultimate repercussions of Bachmann's charged rhetoric are not yet clear. Although few would argue that spreading blatant misinformation should be a punishable offense, false claims about vaccine risk can have deadly consequences when they discourage vaccination [73, 74], so they should not be ignored. To counter the effects of invalid statements, the public health sector must work even harder to educate the public in order to reach vaccination coverage. Whatever one's views on mandates or the cost of the vaccine, its excellent safety record and capacity to benefit human health make protecting the reputation of the HPV vaccine from damaging false claims worthwhile.

Studies show that the influence of accurate information about vaccines is maximized when conveyed from physician to parent or patient [75]. In prioritizing this approach over general health advertisement campaigns, physicians retain their position as patient advocates rather than agents of the government who must enforce policy. Research suggests that physicians are the most influential source of information about vaccines, including the HPV vaccine [76-78], for parents [79, 80]. In fact, some research shows that physicians' attitudes have a larger impact on immunization rates than the media coverage [81]. Ultimately, the decision to vaccinate a child must be based on an informative discussion between a parent and a physician, not on the erroneous claims of political candidates. When public figures imperil the safety of the public with irresponsible claims and fear mongering, it is imperative that both organized medicine and individual physicians speak up.

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HISTORY OF MEDICINE

New Media, Old Messages: Themes in the History of Vaccine Hesitancy and Refusal

Jason L. Schwartz, MBE, AM

The current climate surrounding childhood vaccination in the United States is one of confusion and vitriol. Despite the well-documented achievements of vaccines and extensive efforts by the public health community to ensure their safety, vocal critics of vaccination proffer a growing list of theories that link vaccines to an array of medical conditions, most prominently autism. Others question the necessity of newer vaccines, seeing their arrivals not as triumphs of medical research but as overreaches by a profit-obsessed pharmaceutical industry and an accommodating, financially conflicted medical establishment.

In response to these charges, physicians, scientists, and government public health officials are routinely on the defensive, refuting allegations of unconfirmed risks, justifying the value of recommended vaccines, and striving to preserve public trust in vaccination overall. While national data suggest that a strong foundation of support for vaccination remains, regional clusters of unvaccinated children and increases in nonmedical exemptions from state school-entry vaccination requirements are causes for alarm among advocates of vaccines. Even more worrisome is research suggesting that the safety of vaccines is a growing concern among many parents [1].

The contours of the current debate regarding vaccination may be notable for their novelty—new vaccines, new recommendations, new research evidence, and new trends in diagnoses, to name a few examples. Just as striking, however, are the echoes in contemporary vaccine debates of the history of such movements. At the heart of these conflicts are the complex, long-contested relationships among citizens, science, and the state and their implications for public health policy and practice. The historical antecedents of contemporary vaccine hesitancy and refusal reveal that the present state of affairs is not an unprecedented crisis but an opportunity for renewed education, dialogue, and consensus-building regarding the value of vaccines.

Patterns in the History of Vaccine Opposition

Two primary themes can be seen throughout vaccine opposition movements of the past and present. The first is the perception among critics that vaccines, individually and collectively, cause more harm than the diseases that they are intended to prevent. Even before the introduction of Edward Jenner's smallpox vaccine, Cotton Mather and other advocates of variolation in eighteenth-century New England were forced to defend that immunization practice against such charges. As smallpox vaccination programs eventually contributed to a massive decline in the incidence of the disease

by the early twentieth century, questions about the necessity of continuing to vaccinate grew in frequency and intensity.

This pattern has continued throughout the life cycles of more recent vaccines. Most have been met initially with great enthusiasm, in part because the serious, sometimes fatal consequences of the diseases they prevent had been familiar to the public. As a result of successful vaccination programs, vaccine-preventable diseases and their effects gradually become far less visible. In time, patients, parents, and even many health care professionals have little firsthand familiarity with the diseases that vaccines prevent. The benefits of vaccines are then difficult to discern, while the risks—those known to exist and others that are alleged—become comparatively more visible. Proponents lament that "vaccines are victims of their own success," and opposition to vaccination has been particularly active during these ebbs in the prevalence of vaccine-preventable diseases.

A second theme in this history is the close association between the promotion of vaccines and mandatory vaccination policies intended to ensure compliance. The earliest laws requiring vaccination were introduced in several European cities and Boston within 25 years of the arrival of the smallpox vaccine. By 1827, Boston was the first U.S. city to link compulsory smallpox vaccination with school attendance, a practice that spread throughout the country by the end of the nineteenth century. Enforcement varied widely, particularly between outbreaks, and it declined altogether as smallpox grew exceedingly rare in the United States by the mid-twentieth century. The introduction of several new vaccines beginning in the 1950s, coupled with severe outbreaks of measles among schoolchildren, led to a renewed emphasis on school vaccination requirements in the 1960s and 1970s. These state requirements increasingly included most, if not all, vaccines routinely recommended for school-age children, establishing the model that persists today [2].

Compulsory vaccination has been strongly contested since its earliest appearances. In England, enforcement of a nineteenth-century smallpox requirement disproportionately targeted the working-class and poor with fines and jail terms for noncompliance, provoking an organized opposition movement [3]. Its efforts led to reforms allowing conscientious objections, the forerunner of contemporary exemptions from state vaccination requirements. In the United States, the Anti-Vaccination Society of America was established in 1879, and similar groups in cities brought together like-minded members of diverse religious, ethnic, and socioeconomic groups [4, 5]. They were often joined by medical practitioners whose views were outside the mainstream of their professions.

While the 1905 decision of the Supreme Court in *Jacobson v. Massachusetts* upheld the authority of governments to mandate vaccination (and a 1922 case—*Zucht v. King*—expressly permitted vaccination linked to school attendance), compulsory vaccination remained a source of considerable tension between health authorities and the public. A 1906 news item from York, Pennsylvania, headlined "Vaccination Stirs Revolt," reported, "Threats to burn schoolhouses, whip teachers, and punish school

directors have been the outcome of the enforcing of the compulsory vaccination law" [6]. In one affected school, only 94 of 370 students were in compliance with the requirement. Elsewhere during this period, scuffles with the police over compulsory vaccination were common, providing important context when we speak of contemporary "resistance" to vaccination [7].

By the early 1970s, most state vaccination requirements included newer vaccines such as measles and polio. A 1969 review of mandatory vaccination identified three principal objections voiced by opponents of these policies: government intrusion on religious beliefs, general distrust of medical science, and infringement of personal liberty [8]. These themes capture quite well the major objections of critics to that point, and they remain remarkably apt synopses of critiques of U.S. vaccine policy in 2012.

Contemporary Opposition to Vaccination Policy

Despite the introduction of many new vaccines and concurrent advances in vaccine science and practice, the core arguments of critics of vaccination continue to parallel those expressed for nearly 200 years. They question the science of vaccines—namely, that the risks are greater or the benefits less than the mainstream public health community believes—or assert that the state is inappropriately interfering with individual or parental autonomy by requiring vaccination for school-age children. What has changed are the ways in which parents, scientists, physicians, and others skeptical or critical of vaccines communicate and collaborate.

In contrast to the early history of vaccination, when local, grassroots opposition movements were most prevalent, today's critics of vaccines are part of national and international networks that have capitalized on the explosive growth of information technologies in the past quarter-century. Many observers of this history point to a 1982 television documentary, *DPT: Vaccine Roulette*, as a turning point in the modern history of vaccine safety controversies [9]. The program featured emotional profiles of children believed by their parents to have been harmed by the diphtheria-pertussis-tetanus combination vaccine. In the years that followed, parents with similar stories involving a variety of vaccines and their alleged risks would become a mainstay of popular media coverage of vaccine debates.

Throughout the more recent controversy regarding vaccines and autism, some of these parents or grandparents have been celebrities or public officials, providing a still larger platform for such accounts, absent confirmation that the conditions described were caused or exacerbated by vaccines. Until very recently, the opinions and personal experiences of such critics often received media attention equal to that given to the consensus views of national medical and scientific organizations regarding vaccine safety.

The Internet has been similarly transformative in bringing together individuals and groups critical of vaccines and contemporary vaccine policy. Instead of the pamphlets common to early vaccine opposition movements, web sites, blogs, e-mail

lists, and related media now allow parents to instantly compare their experiences, share theories regarding the causative role of vaccines, and coordinate activism on vaccine safety policies and legislation.

The Internet has also democratized access to scientific and medical knowledge among patients and parents. Despite frustration from some health care professionals, these changes help to promote an environment in which patients are engaged, informed, and active contributors to their own medical decision making. A related change with more mixed outcomes for medical knowledge and patient care is the massive growth in venues available for the publication of scientific research, many of which exist principally or exclusively online. The quality of these publications varies widely; publishing standards may be inconsistent, and peer review limited or nonexistent.

Patients or parents researching vaccines or other health topics may have difficulty distinguishing reputable sources of information from less trustworthy venues. In the case of vaccines, public discourse and public health may be jeopardized by the publication of research so flawed in design or analysis that valid conclusions cannot be reached. Much of the published research cited by proponents of the vaccine-autism link and similar theories has appeared in publications of dubious reputation and is rejected as scientifically unsound by mainstream researchers. However, the most prominent published science on vaccines and autism, the now-retracted 1998 paper by Andrew Wakefield and colleagues, appeared in *The Lancet*, among the world's premier medical journals. The gatekeeping function of scientific publication is not without flaws, but it remains one important safeguard in promoting the dissemination of valid, scientifically responsible research results.

Preserving and Promoting Vaccination in a Democracy

The pace of advances in scientific and medical knowledge today is only surpassed by the speed at which such information can be transmitted. Amid this changing climate, the core arguments of critics of vaccination have remained remarkably stable. Public health officials and other advocates of vaccination have largely focused their efforts on refuting specific claims against the safety and necessity of vaccines and the importance of school-entry requirements. The long-term success of this approach is questionable; recent experience suggests that new hypotheses appear more quickly than they can be conclusively refuted. For example, as evidence mounted against a link between the measles-mumps-rubella vaccine and autism, replacement theories began emerging, alleging that specific vaccine components, the timing and spacing of vaccination, or the overall vaccine schedule may actually be to blame. Maintaining a largely defensive, responsive posture to vaccine safety allegations may ultimately be ineffective.

A superior strategy for advocates of vaccines may be to use the current media and information environment to refocus attention toward the positive case for vaccines. A lesson from the long history of vaccine hesitancy and refusal is that the most strident critics of vaccine safety are unlikely to be swayed by any amount of

evidence, particularly evidence produced by government scientists and academic researchers, groups whom they generally distrust. Meanwhile, growing numbers of parents who are not active participants in vaccine safety movements are expressing new concerns about the risks of vaccines. Directing efforts toward preserving the widespread foundation of support for vaccines that persists despite these controversies may be the most fruitful route to maintaining the success of vaccination programs [10].

Such work requires not merely a communications or marketing strategy by the public health community but a continued commitment to ensuring the safety of vaccines, assessing their benefits for individuals and communities, and implementing mandatory vaccination programs responsibly. Concerns in these areas have motivated opposition movements since the dawn of vaccination. While history suggests that broad consensus on the design and scope of vaccination programs is unlikely to be reached, all participants in these debates can work for respectful dialogue informed by the best available evidence [11]. In this way, citizens, scientists, and public officials can advance both the best ideals of a democracy and the health of its citizens.

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OP-ED

Closing Immunization Gaps in the U.S: How a Little Collusion Could Go a Long Way

Jeremy Konstam

As elucidated in, "New Media, Old Messages: Themes in the History of Vaccine Hesitancy and Refusal," misinformation about vaccines represents a significant hindrance to public health. Falsehoods, once made public, are difficult to counter. Both the national prominence of individuals who espouse misinformation about vaccines and the unified simplicity of their message are at the heart of the problem. Loudly stated misinformation overshadows complex, multisource scientific data in the minds of the American people, and the misinformation sticks.

Research has documented public skepticism regarding vaccine safety. More than half of American adults say they are concerned about the safety of vaccinations for children [1], and about a quarter of parents think that vaccines can cause autism [2]. In perhaps the most telling statistic, only 76 percent of adult respondents to a Research!America survey reported believing that vaccines pose less of a risk than the diseases they are meant to prevent. [3].

Gaps in vaccination coverage seem to follow from these gaps in perception of vaccine safety. According to a recent report, lack of vaccine coverage can be traced directly to a lack of knowledge about the safety and effectiveness of vaccines [4]. Utilization of recommended adult vaccines range from 26 percent to 65 percent [5], and in 2009, nearly 30 percent of U.S. children were not up to date on their vaccinations according to the schedule recommended by the CDC [6]. Trends show that the problem is getting worse. The percentage of parents who refuse or delay vaccinations for their children rose sharply during the last decade, increasing from 22 percent in 2003 to 39 percent in 2008 [7].

Gaps in vaccine utilization have major implications for American health care. The financial burden of vaccine-preventable diseases among adults is about $10 billion annually [4]. The public health burden is equally heavy. As an example, as many as 50,000 to 70,000 adults die annually of pneumonia and influenza in the United States, figures which could be greatly reduced with vaccinations [8].

What can be done about this problem? The Robert Wood Johnson Foundation's "Short on Shots" report offers the following proposals:

- The Centers for Disease Control and Prevention (CDC), as well as state and local health departments, should receive increased resources to create education programs about adult vaccinations.
- Health providers should set an example by complying with recommended vaccinations.
- The National Institutes of Health, the U.S. Food and Drug Administration and the CDC should receive increased resources for vaccine research and development [4].

Of note, two of these three recommendations involve increased appropriations to government agencies, a prospect that seems unlikely in the current fiscal environment. In the near future, federal agencies will be clawing tooth and nail to avoid cuts, not arguing for increased appropriations.

Enter the vaccine companies.

The Vaccine Industry: Big Business and Getting Bigger

Even in the face of the public health challenges outlined above, the vaccine business has become an area of growth for pharmaceutical companies. To quote a recent Associated Press article, "Vaccines are no longer a sleepy, low-profit niche in a booming drug industry. Today, they're starting to give ailing pharmaceutical makers a shot in the arm" [9]. Vaccine sales are expected to double, from $19 billion in 2010 to $39 billion by 2013, according to market research firm Kalorama Information. This growth will amount to a nearly five-fold increase in vaccine sales from 2004 figures [10]. In sum, vaccines now have more value to pharmaceutical companies than ever.

With the growing importance of vaccine sales to their bottom line, private companies now have an increasingly large stake in the success of public education campaigns on vaccine safety. Several companies have gone so far as to launch informational web sites [11, 12] to correct public misperceptions about vaccine safety. Despite the potential value of these sites, the message remains fragmented, and perhaps suspect—user-friendly private sites have obvious conflicts of interest; their goal is to sell vaccines. Government sites, on the other hand, are informative but dry and sometimes difficult to navigate. It is then no surprise that that these efforts to educate the public on vaccine safety continue to be drowned out by clearer, simpler antivaccine messages.

The Bottom Line: A Little Collusion Could Go a Long Way

We've now landed at the root of the misinformation problem: those providing the inaccurate information often have a more penetrating voice than those accurately describing the science of vaccines.

With pharmaceutical companies already spending 32 percent of their revenue on marketing [13], and vaccines emerging as an area of industry growth, why couldn't private firms collaborate with the government to craft the clear, cohesive message

needed to counteract bad information? Why not link private vaccine information web sites together through the CDC's website so that the user-friendly information is also credible? Why can't we make sure that when someone searches "vaccines," "vaccine safety," or "vaccines and autism," this government web site is the first that comes up? Why couldn't the government coordinate with vaccine companies on web design to make the page as user-friendly as the industry's? Why not give the provaccine voice as much name recognition as the antivaccine voice, and use private money to enlist celebrity spokespeople for the government's vaccine education campaign? In short, why not consolidate, or at the very least, coordinate, public and private efforts to implement a more effective vaccine safety education campaign?

In business, just as in government, shared interests are what drive initiatives forward. Our public health agencies and vaccine companies are, in this case, a perfect fit. Where the government sees gaps in immunization coverage, vaccine manufacturing companies see gaps in market coverage. Each group is highly motivated to close these gaps, and each understands that public education is critical to accomplishing its goals.

The bottom line: for public perception to be swayed, vaccine information has to be delivered in the same simple, unified manner that vaccine misinformation is delivered. To accomplish this, public and private efforts to dispel misperceptions about vaccine safety must be coordinated. Such collaboration would produce the clear, cohesive voice of vaccine safety needed to not only reach the minds of the American people, but stick. In this sense, a little "collusion" between the government and vaccine manufacturers could go a long way toward closing gaps in immunization coverage.

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OP-ED

An Ethical Take on the "Stress Vaccine"

Jennifer M. Ladd and Leo D. J. Ungar, MTS

Chronic stress has been linked to severe declines in health and dramatically decreased longevity. It causes the death of neurons in the hippocampus, a region of the brain heavily involved in memory formation [1] and aggravates damage caused by cerebral ischemia in stroke [2, 3]. Prolonged stress suppresses the immune system, leading to compromised wound healing, reactivation of previously latent viral infections, increased susceptibility to new infections, and decreased efficacy of administered vaccines [4, 5]. Chronic stress has also been linked to a host of systemic diseases including obesity, type 2 diabetes, atherosclerosis, and hypertension [4, 6]. Many of these adverse health outcomes are mediated by glucocorticoids, hormones synthesized in the adrenal cortex (for a comprehensive review of glucocorticoid actions in the stress response, see Sapolsky et al. [7]). Therefore, an intervention that attenuated the downstream effects of glucocorticoids might reduce the morbidity and mortality of stress.

Over the last several years, the labs of Drs. Sapolsky and Steinberg, both of Stanford University, devised such an intervention. The result of their groundbreaking work is an inducible vector system, a modified herpes virus that is activated in times of neural insult. One version of the vector system expresses a chimeric protein that blocks the detrimental effects of glucocorticoids by converting them into protective signals, mediated by estrogen, which promote neuronal survival [3]. Another version of this neuroprotective vector system is activated by oxygen deprivation (as in ischemic injury to the brain) or by harmful reactive oxygen species (as in post-ischemic cortical reperfusion damage), and releases neuroprotective factors specific to each injurious process [8]. These novel techniques have been successful thus far only in cell and tissue cultures. Their application to humans is still highly hypothetical. Further research is needed, both to develop the technology to deliver these neuroprotective vectors to humans and to assess safety and efficacy. Still, because some have imagined these vectors being administered as an injection, and protecting against the harmful health effects of stress, this hypothetical intervention is being called a "stress vaccine."

This idea of a stress vaccine is already causing controversy. Some worry that it might be "bad to eliminate feelings of stress" or even that it would be a "brain-eating vaccine" that could "lobotomize, zombify [the] global population" [9]. While the phrasing of these worries is sensationalist, a vaccine that altered not only the health-related sequelae of chronic stress but also the behaviors and judgments resulting from stress gives legitimate ground for concern.

In this paper we discuss the ethical implications of the stress vaccine. We will argue that, while there may seem to be cause for ethical concern about the stress vaccine's impact on behaviors and moral judgment, the similarity of the stress vaccine to already widely accepted stress reduction techniques, as well as considerations of justice, render research to create a stress vaccine ethically endorsable.

First, though, we will consider whether a stress vaccine would in fact alter behaviors and moral judgment and, if so, how.

Would the Stress Vaccine Change Behavior and Moral Judgment?

The stress vaccine would work by interfering with the molecular underpinnings of stress responses, such as the glucocorticoid pathways, to prevent detrimental health outcomes. Yet it is not entirely clear what consequences tinkering with these physiological pathways would have on behaviors. To date, correlations have been observed between a whole conglomerate of physiological processes called the "stress response" (hormone release, changes in neuron functioning, changes in the cardiovascular system, and so on) and stress-related feelings and behaviors. What has not been as well elucidated is exactly which of those physiological processes, or which combination of those physiological processes, leads to which behaviors. This lack of understanding about the mechanisms by which the stress response alters behavior might be due to scientists' inability to isolate individual aspects of the response to stress, or it may be to an in-principle difficulty of measuring changes in some of these behaviors. Thus, although it seems plausible that the stress vaccine could alter behaviors by altering very particular ways in which stress works in the body, this thesis is not fully supported by evidence at this time.

The absence of evidence of the stress vaccine's effect on behaviors does not amount to evidence of an absence of that effect. For that reason, we will speculate about what the stress vaccine's effects on behavior (particularly on performance quality) and on moral judgment might be and whether these possible effects are legitimate cause for concern. We consider the stress vaccine's potential effects on performance enhancement and moral judgment as illustrative examples of its ethically relevant features, but we recognize that they are not the only ethically relevant effects of the stress vaccine on emotion, cognition, and behavior.

Stress and Behavior

While chronic stress leads to significant morbidity and mortality, acute stress is often thought of as a beneficial adaptation to crisis, instrumental to the "fight or flight" response. Importantly, since the vaccine would work by affecting the physiology of the body's response to stress, it might alter not only the health effects of the chronic stress response, but also the potentially performance-enhancing effects of the acute stress response. Some may argue, then, that a cost of the stress vaccine's improving health outcomes in the long term could be the loss or dampening of acute stress response's short-term behavioral benefits.

The problem with this argument, however, is that the research on this topic is decidedly divided. The effects of acute stress on performance seem to be highly context-specific and individual, and there is no consensus about whether the change in behavior is valuable or detrimental. Some research shows that acute stress improves performance in certain situations. One study, for example, linked acute stress to enhanced spatial navigation abilities [10]. In another study, acute stress mediators led to an improved ability to recall emotionally salient images [11].

Yet substantial research leans in the opposite direction. Some studies point to a decrease in team performance in times of acute stress, during which members of a team are less likely to communicate effectively and utilize each other's expertise [12]. Other investigations have determined that acute stress may decrease working memory, weaken the capacity to perform discrete complex tasks, and impair the ability to multitask effectively [13]. Highly sharpened focus could be beneficial in situations of acute danger where intense effort is required, but it could also lead to the neglect of other salient features of a crisis. Whether acute stress is performance-enhancing or performance-diminishing seems to depend on the nature and context of the performance in question and on the individual.

It is unclear how exactly the chronic stress vaccine might influence the acute stress response and its sequelae, and the lack of exact data warrants future research on the stress vaccine's effect on behavior. Therefore, there currently seems to be insufficient evidence for the immediate rejection or approval of the vaccine on behavior modification-related ethical grounds.

Stress and Moral Judgment

The field of ethics has long recognized two distinct approaches to assessing whether a given action is considered morally good or morally bad—the deontological approach and the consequentialist approach. Deontological judgments derive from the thesis that what makes actions morally good or bad is how well or poorly those actions follow certain moral rules. Consequentialist judgments instead derive from the thesis that what makes actions good or bad is the goodness or badness of those actions' consequences.

A developing literature in moral psychology supports the conclusion that deontological judgments tend to be driven by emotional processes whereas consequentialist judgments tend to be driven by more "cognitive" processes [14, 15]. If we think that stress tends to elicit emotional responses and suppress "cognitive" processes, it could favor deontological over consequentialist judgment. Conversely, the stress vaccine, by interfering with stress-elicited emotions, could favor consequentialist over deontological judgment. Such a link between the stress vaccine and moral judgment is, however, highly speculative.

Up to this point, we have outlined how the stress vaccine works and how it may impinge upon behaviors and moral judgment. We have noted that, while these potential effects of the stress vaccine are speculative, they merit follow-up and

should not be considered unambiguously problematic. We believe that the potential effects of stress on behavior and moral judgment are not reasons in and of themselves to discourage further research on the stress vaccine.

We will now turn to what we think are the two strongest reasons, beyond beneficial health effects, to support this new technology: that the vaccine is similar to interventions we already widely accept and that the vaccine is defensible from the perspective of justice.

The Stress Vaccine and Existing Stress-Reduction Techniques

While the stress vaccine may seem to raise novel ethical concerns, we already use other techniques to modulate stress and its effects. Exercise, yoga, and meditation are among the most widely used and accepted, and numerous studies have documented that these methods do in fact reduce stress. For example, mindfulness meditation techniques have been linked to a decrease in negative feelings associated with stress [16]. Another practice shown to reduce such feelings is tai chi, both because it requires moderate physical activity and because of its meditative aspect [17]. Other studies have gone further, demonstrating not only that exercise reduces feelings of stress, but also that it combats other results of stress such as poor memory and physical sequelae [18, 19]. Mindfulness-based methods for stress reduction, moreover, have been shown to effectively promote coping behaviors and reduce some adverse mental and physical effects of stress [20]. Finally, meditation has even been shown to directly decrease levels of glucocorticoids in the blood [21], thus mediating many of the biological responses to stress.

The challenge to those who would judge the stress vaccine to be different than exercise and meditation, then, is to identify some ethically relevant difference between the two. No such difference is immediately evident.

One may worry that an ethically relevant difference between the stress vaccine and widely accepted interventions is different physiological mechanisms underlying the effects of each. However, as noted above, studies have shown that meditation acts on glucocorticoid-mediated pathways, the same pathways on which the stress vaccine acts.

It also seems implausible, for example, that there is an ethically relevant difference between exercise and the stress vaccine with regard to the delivery of each. It does not seem like an ethically relevant fact that one is a recreational activity that is self-motivated or instructor-supervised and the other would be an injection administered after fully informed consent by a physician.

Further, it seems unlikely that there are ethically relevant differences between exercise and the stress vaccine in their duration and degree of suppression of the effects of stress. One might be concerned that the stress vaccine's suppression of the effects of stress could be greater and longer lasting than that of exercise. However, someone on a longstanding exercise or meditation regimen could achieve strong

long-term stress suppression, but the length of this effect would certainly not be reason to conclude that exercise or meditation are ethically objectionable. Therefore, it cannot be the stress vaccine's hypothetical potential for longer-term suppression of the stress response that renders it ethically different from exercise and meditation since these practices too could have strong long-term effects.

Therefore, it seems difficult to conclude that the stress vaccine is worrisome without having to conclude the same about widely accepted practices. There are differences between the stress vaccine and accepted practices, but these differences do not seem to be ethically relevant.

In fact, the stress vaccine might even be better than these other practices based on an essential ethical metric—justice.

Who Would the Stress Vaccine Benefit Most?

Since the stress vaccine would work by altering stress physiology, it may work best in people who have the highest levels of glucocorticoids and glucocorticoid-related health pathology. Those who are sickest and under the most stress may benefit most, and some scientific research shows that these individuals may also tend to be at the bottom of societal hierarchies. In certain hierarchies, baboons at the lowest rungs of the social ladder have been shown to possess higher levels of stress hormones and suffer greater stress-induced health damages [22]. Extending these results to humans, the Whitehall Study revealed not only that social status predicts health outcomes in workers employed by the British Civil Service, but also, strikingly, that health in this population varies along a social gradient, with executives the healthiest and longest lived, and every step down the social ladder conferring greater morbidity and mortality [23, 24]. The mechanism underlying this social gradation in health outcomes has not been fully elucidated, but has been linked to feelings of "low job control," a psychosocial factor that could in turn be linked to health through stress-mediated pathways [25]. If this mechanism is correct, then at least in certain hierarchies, the people who would benefit most from a stress vaccine may be those at the bottom of the hierarchy, since they would be have the most stress-caused pathology.

This feature of the stress vaccine is ethically important because, according to many theories, benefits to those who are worse off are more ethically justifiable than benefits to those who are better off. Different ethical theories arrive at this conclusion in different ways. According to egalitarian theories, benefits to those who are worse off are good because they reduce inequality [26]. According to prioritarian theories, benefits to those who are worse off are good, not because they reduce inequality (although they may), but precisely because they are benefits to those who are worse off [27, 28]. According to more than one ethical theory, then, a feature of the stress vaccine that counts towards its being morally good is that the benefits it promises might be greatest for those who are worse off to begin with.

Nevertheless, it could be argued that those who would benefit most from the vaccine might have the least access due to its cost or distribution. According to this concern, if the vaccine became more available to the comparatively rich, it could exacerbate inequality. This worry is not unique to the stress vaccine, however. It can be applied to all medical innovations. Indeed, it can be applied to all of medicine. Medical care is unequally distributed. This may be reason to think that medical care should be distributed differently, but this is certainly not a reason to conclude that medical care itself is morally bad. Similarly, concerns about the stress vaccine's inequitable distribution are concerns about the system that would determine its relative availability, not about the vaccine itself.

Another equality-related concern about the stress vaccine could be that getting it could confer some stigma, marking one as more stress-prone. Again, though, this concern is not unique to the stress vaccine. For example, it is applicable to psychiatric care, which is sometimes thought to confer stigma. However, because being the recipient of a given psychiatric intervention (such as antidepressants) can confer stigma does not mean that the psychiatric intervention is itself morally wrong. Perhaps the stress vaccine's potential to confer stigma on those who take it is reason to advocate for strict privacy protections. But it is not reason to conclude that use of the vaccine is itself unethical.

Overall, then, is the stress vaccine, and research toward it, ethical? The health consequences of chronic stress are real and severe. The possibility of alleviating these health problems is a strong impetus to develop and utilize a stress vaccine. However, while the vaccine seems indicated from a purely medical standpoint, the ethics of its development and use are controversial. The stress vaccine's potential to alter behaviors and moral judgment may be cause for ethical worry, but these concerns do not outweigh the benefits of the stress vaccine's capacity to promote justice.

Perhaps most importantly, we do not find an ethically relevant difference between the stress vaccine and already accepted stress-reduction practices such as meditation. While we recommend that scientists continue to explore the effects of the stress vaccine beyond those narrowly limited to health, and while we recommend that ethicists continue to consider the stress vaccines' broader implications, we conclude that research to create a stress vaccine, in addition to being scientifically laudable and medically beneficial, is, at least tentatively, ethically endorsable.

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