

# The Promise of Vaccines: The Science and the Controversy

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## Executive Summary

Standing among the greatest achievements in public health, vaccines have had a greater impact on reducing death and disability from infectious diseases than almost any other public health intervention. This paper presents a comprehensive overview of vaccines and the science of immunity, including a discussion of the remarkable advances in disease prevention through the evolution of vaccines. We focus on several recent vaccine safety controversies that may prevent maximization of their potential.

Much attention has been devoted to vaccine safety and the potential relationship between various diseases and vaccinations, including the rotavirus vaccine and intussusception, influenza vaccine and Guillain-Barré syndrome, MMR (mumps, measles, and rubella) vaccine and autism and idiopathic thrombocytopenia purpura, hepatitis B vaccine and multiple sclerosis, Lyme disease vaccine and rheumatoid arthritis, and childhood vaccines and type 1 diabetes. The vast majority of reports linking vaccines with various diseases comprise case reports that do not meet the scientific criteria established to attribute causality. A review of recent studies published in the medical literature is presented to help clarify the scientific data related to the association between vaccines and these medical diagnoses. Also addressed are concerns about safety related to vaccine additives and preservatives, specifically thimerosal.

A serious public health issue related to vaccines involves the concept of community immunity (previously known as “herd immunity”) and the risk of disease resurgence related to both the erosion of coverage in at-risk individuals and communities, and to recent policy trends towards philosophical exemptions for vaccinations. The measles epidemic of 1989 to 1991 clearly demonstrates the public health risk when coverage levels fall. Conversely, the potential for success in disease prevention is illustrated by the rapid decline in the incidence of invasive *Haemophilus influenzae* type b after the introduction of the conjugate Hib vaccine, which has become one of the most compelling success stories in modern immunization practice.

In order to guarantee vaccine safety, maintain public confidence, and ensure the continued development of vaccines, a system of checks and balances is essential. The safety systems that involve collaborative efforts between the U.S. Food and Drug Administration, the Department of Health and Human Services, and the Centers for Disease Control and Prevention, and the creation of the Vaccine Adverse Events Reporting

System (VAERS), the Clinical Immunization Safety Assessment Centers (CISA), and the Vaccine Safety Datalink (VSD) are described.

Although our nation's commitment to improving coverage levels and eliminating vaccine-preventable diseases faces many challenges, vaccine science holds the possibility of targeting an increasing number of diseases for prevention, with the number of vaccines in widespread use projected to grow to over three times the current number by 2020.<sup>3</sup> This story of our nation's progress towards eradicating vaccine-preventable diseases holds many lessons for the future and attempts to address several key questions: How well are we preventing diseases through vaccination? How safe are vaccinations? Is the public at risk because of erosion of coverage and because of philosophical exemptions? What challenges does the nation face as we attempt to improve vaccine coverage and eliminate vaccine-preventable diseases?

## Introduction

Among the greatest achievements in public health has been the advent of immunization.<sup>1</sup> Beginning with the seminal work of Edward Jenner over 200 years ago, vaccines have had a greater impact on reducing death and disability from infectious diseases than almost any other public health intervention. Vaccines additionally are one of the most cost-effective tools in the arsenal of modern medicine.<sup>2</sup> Certain barriers such as complacency remain that prevent the maximization of the potential and the promise found within the science of vaccines.

Even as the number of illnesses and deaths due to vaccine-preventable diseases decline in the United States, controversy has developed regarding the safety of vaccines. New vaccines and vaccine combinations that provide a wider array of protection from infectious diseases *may* require more injections and greater complexity in the immunization schedule. This rapid evolution in the development of new vaccines and the potential for adding additional vaccines heightens concerns for safety at a time of relatively low rates of vaccine-preventable disease.<sup>3,4</sup> Conversely, during periods of higher incidence of vaccine-preventable diseases and outbreaks, safety concerns appear to be less prevalent.

As with other pharmaceutical products, vaccines can produce side effects, most of which are local injection-site reactions and low-grade fevers. Rarely, serious adverse events are reported such as paralytic polio in immunocompromised children, intussusception post rotavirus vaccine and Guillain-Barré syndrome post influenza vaccine administration.<sup>10</sup> Over time, the formulation of certain vaccines (whole cell per-

tussis) or the recommended type of vaccine (live attenuated poliovirus) has been altered specifically because of a system of checks and balances that exists to assure efficacy and safety.

Over the last several years, reports have appeared in the lay press and some journals about the association between vaccines and a wide array of diagnoses such as autism, autoimmune disorders, diabetes and sudden infant death syndrome (SIDS). The vast majority of these reports comprise case reports that do not meet the scientific criteria established to attribute causality, yet concerns persist. Large-linked data base studies have helped to clarify concerns and in rare instances support actions to remove vaccine products from the market. Removal of the rotavirus vaccine from the market is a recent example of the effectiveness of this system.

Public policy makers have on occasion responded to case reports and media coverage with recommendations for liberalizing personal and philosophical exemptions from mandated childhood vaccinations. Recent studies indicate that such policies may place communities and individuals at increased risk for vaccine-preventable diseases because of increases in the unimmunized population.<sup>7,8</sup> “Community immunity” (the indirect protection of a community from disease because of the high proportion of individuals fully immunized, historically referred to as “herd immunity”) is lost when coverage levels fall.<sup>9</sup> Research and development of new vaccines may face difficulties in funding and support if these trends in policy persist, thus diminishing the potential of vaccines to provide effective protection.

Worldwide it is estimated that over two million children die annually from infectious diseases that could be prevented through timely immunization. In the United States over 50,000 adults and approximately 300 children die annually from vaccine-preventable diseases.<sup>1,3</sup> It is sobering to note that despite all of our scientific and technical advances, only one disease—smallpox—has succumbed to vaccination while the prospect for global eradication of polio is within our grasp.

## History

Vaccination is the active transfer of antigen to effect an immune response in the host that will subsequently prevent infection from a specific bacteria or virus. In the last 200 years vaccines have significantly reduced morbidity and mortality from eleven<sup>11</sup> infectious agents: small pox, diphtheria, tetanus, yellow fever, pertussis, *Haemophilus influenzae* type b, poliomyelitis, measles, mumps, rubella and hepatitis B. In addi-

tion, substantial progress is being made against varicella,<sup>5</sup> influenza, and pneumococcus.

Efforts to vaccinate humans pre-dated the work of Edward Jenner. In the 16<sup>th</sup> and 17<sup>th</sup> centuries medical literature described the use of variolation to protect against smallpox infection. Variolation was accomplished by placing dried pus from the smallpox vesicles into the skin of a susceptible individual.<sup>10</sup> It was hoped that the dried pus would be less infectious and confer protection to the vaccinated individual. Variolation success rates varied greatly and as a result of the use of dried infectious materials, infections occurred. Analysis of this experience would later lead to the concepts of attenuated or weakened vaccines and later killed vaccines, which could not transmit the disease from which one was seeking protection.<sup>10</sup>

Vaccine is derived from the Latin word for cow, “vacca.” This terminology evolved from the practice of injecting material from the vesicles of cowpox blisters of the udders of infected cows into humans. In 18<sup>th</sup> century England, this practice was observed to provide inoculated susceptible individuals protection from infection with the smallpox virus. This type of vaccine would be later designated a type of species variant vaccine that provides crossover protection from one species, cattle, infected with the cowpox virus, to humans exposed to smallpox.<sup>10</sup>

Edward Jenner is largely credited with the first scientifically controlled efforts designed to prevent the spread of an infectious agent. His groundbreaking work was published in 1798 as “Variola Vaccinae.” (It seems, however, that a cattle breeder from England, Benjamin Jesty, may have actually been the originator of the cowpox theory in 1774) Of interest, it was Jenner who recognized in 1810 that the immunity conferred by vaccination was not lifelong.

In 1879, Louis Pasteur further elucidated the concept of attenuation with his work on chicken cholera. He theorized that a weakened strain of the organism would be far safer than the wild strain. Later, Pasteur’s work would lead to the first vaccination of humans against rabies in 1885 with a chemically attenuated rabies vaccine. By 1886 another major milestone in immunization history occurred when Edmund Salmon and Theobald Smith developed a killed vaccine, the killed hog cholera vaccine. The pathogen in this case, a bacteria, was killed by heat.<sup>10</sup>

Paralytic polio became a significant public health concern in northern Europe in the 19<sup>th</sup> century. In the United States during the early 1950s the incidence of poliomyelitis exceeded 20 per 100,000 population, a rate lower than that observed for other infectious agents

such as measles and varicella. Nevertheless, Jonas Salk's introduction of a formalin-inactivated poliovirus vaccine for large-scale clinical trials in 1954 was hailed as a major breakthrough in public health. The vaccine proved to be safe, as well as having an overall efficacy of approximately 70 percent.<sup>10</sup>

During this same period Albert Sabin and others worked to develop the first live attenuated polio vaccine. Attenuation was accomplished after passage or growth of the live (wild) virus in non-nervous system tissue cultures such as kidney cells. The oral live attenuated vaccine provided a less expensive alternative to the injectable vaccine, and offered protection at the serologic and intestinal level against poliomyelitis. By 1964 the Committee on the Control of Infectious Diseases of the American Academy of Pediatrics had indicated a preference for the oral vaccine. Recent studies (1991) have estimated a 90-percent effectiveness in preventing paralytic disease with three doses of oral polio vaccine (OPV).<sup>10</sup>

While great progress has been made in the development and application of vaccines in the last 200 years (*see Table 1*), the next decade has the potential to accelerate the protective efficacy of vaccines for adults and children. New genetic techniques in vaccine manufacturing are being utilized to target infectious agents, and now even cancer has become a realistic vaccine target.<sup>3</sup>

### What Is a Vaccine?

Vaccines can be subdivided into two broad categories, active and passive vaccines.<sup>10,13</sup> The goal of active vaccination is to place a "foreign" substance into the susceptible individual with the intent of inducing an immune response through the production of specific antibodies, a cellular immune response, or both. Passive vaccines generally contain antibodies in the form of immunoglobulins designed to kill or incapacitate an organism. Passive vaccines are most effective when administered as close as possible to the time of exposure to the infectious agent.<sup>10</sup>

The categories of active vaccines include live vaccines, non-live vaccines and DNA-based vaccines (*see Table 2*). Live vaccines are attenuated and are able to replicate in the host thus mimicking a natural infection. In general live vaccines provide a stronger immune response than non-live vaccines. Non-live vaccines are also referred to as killed, inactivated or subunit vaccine and are unable to replicate in the host. Non-live vaccines are frequently less immunogenic in the host. DNA-based vaccines enter the host's cells and create a template for the pro-

Table 1: Outline of the Development of Human Vaccines

	Live Attenuated	Killed Whole Organism	Purified Protein or Polysaccharide	Genetically Engineered
18 <sup>th</sup> Century	Smallpox, 1798			
19 <sup>th</sup> Century	Rabies, 1885	Typhoid, 1896 Cholera, 1896 Plague, 1897		
Early 20 <sup>th</sup> Century	Bacille Calmette-Guérin, 192 (tuberculosis) Yellow fever, 1935	Pertussis, 1926 Influenza, 1936 Rickettsia, 1938	Diphtheria, 1923 Tetanus, 1927	
After World War II	Cell Culture Polio (oral) Measles Mumps Rubella Adenovirus Typhoid ( <i>Salmonella</i> Ty21a) Varicella	Polio (injected) Rabies (new) Japanese encephalitis Hepatitis A	Pneumococcus Meningococcus <i>Haemophilus influenzae</i> PRP* Hepatitis B (plasma derived) Tick-borne encephalitis <i>H. influenzae</i> PRP-protein (conjugate) Typhoid-Vi Acellular pertussis	Hepatitis B recombinant (Yeast- or mammalian cell- derived)

\* PRP: phosphorylribitol phosphate

Table 2: Categories of Active Vaccines

Live attenuated vaccines	Non-live vaccines	DNA-based vaccines
MMR	Pertussis	
Varicella	Polio virus (injectable)	<i>S. flexneri</i>
Rotavirus	Influenza vaccine	Fowl pox virus
Oral polio	Rabies	
Adenovirus	Hepatitis A	
Hepatitis B	Diphtheria	
	Lyme Disease	
	Tetanus	
	Pneumococcal	
	Meningococcal	
	<i>Haemophilus influenzae</i> type b	

duction of vaccine specific antigens.

Live vaccines can be further subdivided based upon the technology utilized to attenuate the pathogenic strain. These sub classifications include such methodologies as attenuation in cell culture (e.g. oral polio vaccine); cold adaptation (e.g., influenza and parainfluenza); variants of viruses in other species (e.g. smallpox vaccine and rhesus rotavirus); reassorted genomes (e.g. live attenuated influenza and rotavirus); temperature sensitive mutants—viral mutations unable to grow at physiologic temperatures (e.g. respiratory syncytial virus vaccine in development); and recombinant vaccines (e.g. herpes simplex vaccine).<sup>10</sup> Additionally, recent genome technology has been employed to enable viruses to carry “foreign” pieces of genetic material. This “foreign” genome can encode for intracellular manufacture of components of pathogens such as proteins.

Non-live vaccines are frequently not as immunogenic as live vaccines but importantly cannot multiply within the host. This relatively lower level of immune protection relative to live vaccines results in the need for booster doses. In order to enhance immunogenicity, non-live vaccines are often combined with an adjuvant (immune-response enhancer) such as aluminum salts. Categories of non-live vaccines include whole pathogen vaccines (e.g., *Bordetella pertussis*, injectable polio vaccine and influenza vaccine); protein-based vaccines (e.g.

Hepatitis B vaccine); peptide-based vaccines; and polysaccharide-based vaccines (e.g., meningococcal and pneumococcal vaccines). Polysaccharide-based vaccines may be conjugated to a protein and examples include *Haemophilus influenzae* type b, meningococcal vaccine and pneumococcal vaccines.<sup>10</sup>

Toxoids are non-live vaccines derived from toxins produced by the pathogen. Diphtheria and tetanus are two toxoid vaccines derived from toxins. Treating the toxin with an adjuvant (such as an aluminum salt) is a technique often used to create a toxoid. Toxoids frequently induce lower levels of immunity and also require a booster on a periodic basis.

### Vaccine Components

A variety of components are added to or present in vaccines. Adjuvants (as previously noted) are utilized to enhance the immune response. Presently, the Food and Drug Administration licenses only aluminum salts for use as adjuvants. Antibiotics are frequently employed during the production process in order to help eliminate microbial contaminants. Multidose vials require that preservatives be utilized in order to reduce the likelihood of contamination during re-use between patients. Thimerosal, an ethyl mercury salt, is an effective preservative that has been in use since the 1930s and is currently used in over 30 US-licensed vaccines.<sup>14</sup> Recent concerns about the cumulative mercury exposure in children have resulted in a substantial reduction (over 70 percent) of childhood vaccines containing thimerosal.<sup>11</sup> The goal of the American Academy of Pediatrics and the CDC is to virtually eliminate the use of thimerosal in the next 1-2 years.<sup>11,12</sup>

Stabilizers are used to protect vaccine integrity from changes in temperature while maintaining immunogenicity. Magnesium salts are commonly used in preparations such as oral polio vaccine for this purpose. As a result of the process utilized in developing vaccines, such as cell cultures, residues may remain. Some vaccines are lyophilized, or freeze-dried, for ease of shipping, handling and storage.

### The Immune Science of Vaccines

The human immune system is characterized by its ability to respond both non-specifically and specifically to foreign substances such as the antigens in vaccines. The non-specific or innate immune response involves the activation of several specialized cell types, including macrophages, neutrophils, natural killer cells, mannose binding

lectins (serum proteins) and cellular products such as cytokines. This non-specific immune response is activated when a person is exposed to any infectious agent.

The specific, or adaptive, component of the immune system confers immunity through its ability to respond to specific substances and has the capacity for memory.<sup>13</sup> The cellular workhorse that responds to these specific stimuli is the lymphocyte, and it is responsible for two broad categories of immune response classified as humoral and cellular immunity.

### *Humoral Immune Response*

The humoral response is characterized by the recognition of antigens by immunoglobulin receptors on B-lymphocytes. After recognition, further differentiation occurs at the cellular level and a plasma cell is formed which produces and secretes antibodies (IgA, IgE, IgG, IgM). Secreted antibodies circulate throughout the body and act independently of the plasma cell.

### *Cellular Immune Response*

T cell lymphocytes respond to foreign stimuli through a variety of mechanisms known as the cell mediated response. T cells represent a more diverse cell line than B cells. Two major classes of T cells exist: CD4, or helper T cells and CD8, or cytotoxic T cells. T cells play a predominant role in the control and elimination of many infections, as they circulate freely and are the initial component of the adaptive immune system to respond to an infectious agent.

### *Community Immunity*

If the level of vaccine coverage, i.e. the percentage of population fully immunized, is sufficient to prevent the spread of an infectious pathogen throughout a community even though some individuals are not immunized, indirect protection is conveyed to the entire community. This type of community-based protection that results from the disruption of transmission between susceptible individuals is called community immunity. If vaccine coverage falls to a level where transmission of the infectious agent is not halted, the entire unvaccinated population is at risk. The measles outbreak of 1989 and 1991 in the United States resulted from falling immunization coverage rates and the loss of community immunity.<sup>3</sup>

The value of community immunity is reinforced by a recent study published by Thomas Reichert and others in the *New England Journal of Medicine*.<sup>9</sup> This study analyzed a mandatory influenza vaccination

Table 3: Changes in Childhood Vaccination Schedule

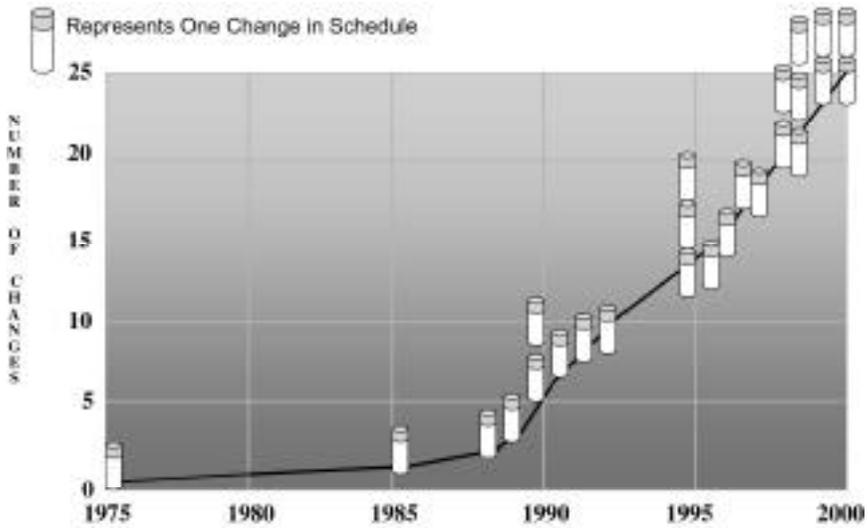


Table 4: Recommended Childhood Immunization Schedule United States, January–December 2001

Vaccines are listed under routinely recommended ages. BARS indicate range of recommended ages for immunization. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible. OVALS indicate vaccines to be given if previously recommended doses were missed or given earlier than the recommended minimum age.

AGE VACCINE	Birth	1 mo	2 mos	4 mos	6	12 mos	15 mos	18 mos	24 mos	4-6 yrs	11-12 yrs	14-18 yrs
Hepatitis B	Hep B #1											
Diphtheria, Tetanus, Pertussis		Hep B #2		DTaP	DTaP	DTaP	DTaP			DTaP	Td	
H. influenzae type b		Hib	Hib	Hib		Hib						
Inactivated Polio		IPV	IPV	IPV		IPV				IP		
Pneumococcal Conjugate		PCV	PCV	PCV		PCV						
Measles, Mumps, Rubella						MMR				MMR	MMR	
Varicella						Var					Var	
Hepatitis A									Hep A: in selected areas			

Approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

program implemented in Japan for school children in 1962 and continued through 1987. The goal of that program was to confer influenza protection to school-aged children and to reduce transmission to the elderly and those at-risk (community immunity). During this period immunization coverage levels for influenza in Japanese children was reported at levels of 50 percent to 85 percent. It was found that influenza infection rates (and death rates) fell markedly during this period in the older population who had not been immunized.

In 1987 parents were given the option to refuse vaccination against influenza and in 1994 the program was discontinued altogether after several reports of adverse events were alleged to be related to the influenza vaccine. As a result of this policy change, coverage for influenza vaccine fell dramatically. The authors emphasized that the percentage of elderly living in homes with young children in Japan is high. The study projects that 37,000 to 40,000 excess deaths in the elderly were prevented annually because of the immunization policy in place from 1962 to 1987. They further conclude that for every 420 children immunized, one death was prevented. These gains were lost when the immunization of school-aged children was eliminated in 1994.<sup>9</sup>

### The Vaccine Schedule

The American Academy of Pediatrics issued their first immunization guidelines in the 1930s. As a result of scientific and technologic advances the recommended schedule has been routinely updated since that initial release. Over the last decade the addition of new vaccines and new vaccine combinations to the immunization schedule has accelerated dramatically. Three childhood and two adult vaccines comprising nine antigens were added to the schedule from 1938 through 1985. Over the next 15 years the number of recommended vaccines more than doubled<sup>3,10</sup> (see Table 3).

In the mid-1990s the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the Advisory Committee on Immunization Practice (ACIP) responded to confusion and criticism over the number and variation of immunization guidelines and established a harmonized childhood immunization schedule (see Table 4). According to the new harmonized schedule children must receive 15 to 19 doses of vaccine before the age of 18 months and a total of 19 to 22 doses in order to be fully immunized by the age of six. In addition, a new pediatric conjugate pneumococcal vaccine was approved for children under the age of two years and for at-risk children

Table 5: Universally Recommended Vaccinations

Population	Vaccination	Dosage
All young children	Measles, mumps, rubella	2 doses
	Diphtheria-tetanus toxoid and pertussis vaccine	5 doses 4 doses
	Poliomyelitis	3-4 doses
	<i>Haemophilus influenzae</i> type b <sup>1</sup>	3 doses
	Hepatitis B	1 dose
	Varicella	2 doses
	Hepatitis A (in selected areas) <sup>2</sup>	
Previously unvaccinated or partially vaccinated adolescents	Hepatitis B <sup>3</sup>	3 doses total
	Varicella	If no previous history of varicella, 1 dose for children aged < 12 years, 2 doses for children aged 13 years
	Mumps, measles, and rubella Tetanus-diphtheria toxoid	2 doses, total If not vaccinated during previous 5 years, 1 combined booster during ages 11-16 years
All adults	Tetanus-diphtheria	1 dose administered every 10 years
All adults aged 65 <sup>4</sup>	Influenza	1 dose administered annually
	Pneumococcal	1 dose

<sup>1</sup> Only children below age 5 receive *Haemophilus influenzae* type b.

<sup>2</sup> Hepatitis A was added to the schedule after the original table's publication.

<sup>3</sup> An optional two-dose schedule for adolescents aged 11 to 15 was recently approved by the U.S. Food and Drug Administration.

<sup>4</sup> The Advisory Committee on Immunization Practices has recommended that all adults aged 50 receive an influenza vaccination.

less than five years of age.<sup>3</sup>

Adolescents need to have a tetanus booster between the ages of 11 to 15, as well as the MMR, varicella and Hepatitis B vaccine if these antigens were missed at an earlier age. The meningococcal vaccine is now recommended for college students living in dormitories.

Adult immunization recommendations have been updated by the ACIP. It is now recommended that adults over the age of 50 receive an annual influenza vaccine. The ACIP is currently reviewing a proposal to lower the recommended age requirement for a one-time pneumococcal vaccine from age 65 to age 50.<sup>3</sup> Influenza vaccine and pneumococcal vaccines are also recommended for younger adults with certain at-risk conditions such as chronic lung and heart disease and for those individuals with a compromised immune system (see Table 5).

In the last several years, significant changes have been made in the immunization schedule.<sup>3,15</sup> These include those indicated below.

- 1995: Licensure of the varicella vaccine
- 1996: Hepatitis A recommended for use in several states and regions
- 1999: Rotavirus vaccine added to the childhood schedule, then removed due to increased risk for intussusception
- 1999: Inactivated polio vaccine (IPV) recommended for the first two doses of polio vaccination
- 2000: DTaP, an acellular form of pertussis recommended to replace DTP
- 2000: IPV recommended for all four doses of poliovirus vaccination
- 2000: Conjugate pneumococcal vaccine approved for children under 2 years of age

Over the next 20 years it is estimated that the number of vaccines could triple<sup>3</sup> (see Table 6). According to a 1999 Institute of Medicine publication the number of recommended vaccines could exceed 54 by the year 2020.<sup>3</sup> Many of the new vaccines will target adult as well as childhood diseases. In addition, the combination of antigens will increase the complexity of schedules while attempting to minimize the number of injections. New delivery modalities such as transdermal and intranasal will be tested and introduced. A nasal spray influenza vaccine will go before the FDA in the very near future and may soon be in the marketplace.

Table 6: Vaccines in Widespread Use, 1985–2020

1985	2000	2020_
Adult influenza	Adult influenza	Adult influenza
Adult pneumococcal polysaccharide	Adult pneumococcal polysaccharide	Adult pneumococcal polysaccharide
Diphtheria, pertussis, tetanus, and components	Diphtheria, tetanus, acellular pertussis, and components	DTaP
Measles, mumps and rubella	MMR	Measles, mumps, rubella, and varicella
Oral poliovirus	Inactivated poliovirus	Eradication of polio expected
	H. influenzae type b	Hib
	Hepatitis A	Hepatitis A
	Hepatitis B	Hepatitis B
	Varicella	Varicella with MMR
	Pediatric conjugate of pneumococcal polysaccharide	Pediatric conjugate of pneumococcal polysaccharide
	<i>Borrelia burgdorferi</i>	<i>Borrelia burgdorferi</i>
	Meningococcal polysaccharide A,C,Y,W-135	Meningococcal polysaccharide A,B,C,Y,W-135
		Adult tetanus, diphtheria, acellular pertussis, and components
		Chlamydia
		Coccidioides immitis
		Cytomegalovirus
		Enterotoxigenic E. coli
		Epstein-Barr
		<i>Helicobacter pylori</i>
		Hepatitis C
		Herpes simplex
		Histoplasma capsulatum
		Human Papillomavirus
		Child influenza

Table 6: Vaccines in Widespread Use, 1985–2020 (continued)

1985	2000	2020
		Insulin-dependent diabetes mellitus (therapeutic) Melanoma (therapeutic) Multiple sclerosis (therapeutic) Mycobacterium tuberculosis Neisseria gonorrhoea Neisseria meningitidis B Parainfluenza Respiratory syncytial virus Rheumatoid arthritis (therapeutic) Rotavirus Shigella Streptococcus, Group A Streptococcus, Group B

Priority candidate vaccines, drawn from IOM, 1999b.

Vaccines covered by Vaccines for Children (VFC) as of February 2000.

Vaccines likely to be recommended for universal use (including VFC coverage for childhood vaccines).

### The Syndromes and the Suspects

Some “consumer” and parents groups have, in recent years, attributed a variety of syndromes and disease outcomes to the use of vaccines.<sup>4,16–19</sup> As with any pharmaceutical, adverse events attributable to vaccines do occur. The large majority of these events are local reactions at the site of injection or low-grade fevers. In rare instances, serious adverse events are reported, such as paralytic polio after the administration of live attenuated oral poliovirus to immunocompromised and immune intact children and intussusception following rotavirus vaccine. The risk of vaccine associated paralytic polio in the United States was approximately one case per 2.4 million doses of oral polio administered.<sup>10</sup>

As the number of vaccine antigens and vaccine combinations expands and infections due to vaccine preventable diseases decline, concerns about the association between a number of medical diagnoses and vaccines have increased. Given the relatively high rate of immunization

coverage both in the United States and abroad the likelihood that individuals with a variety of illnesses such as autoimmune diseases, type 1 diabetes, and autism concomitantly having a history of immunization is not surprising. Additionally, the clinical tools now available to diagnose diseases more precisely and earlier have led to the perception that some illnesses are on the rise.<sup>4,16</sup> Finally, public awareness of vaccine safety has been increased through mass media, concerned policy makers, alterations in the physician-patient relationship, and expanded use of the Internet. These same modalities often fail to supply the necessary perspective: that hundreds of thousands of individuals received the same protective vaccines without any adverse events.<sup>16</sup>

During the last several decades a variety of diagnoses have been postulated to be causally linked to vaccination. In 1976 recipients of the “swine influenza” vaccine were noted to have an eight-fold increased risk of Guillain-Barré syndrome.<sup>10,20</sup> Recently concern has focused on the association between childhood immunizations and type 1 diabetes mellitus, Hepatitis B and multiple sclerosis; MMR and autism and idiopathic thrombocytopenia purpura; Lyme Disease vaccine and rheumatoid arthritis; and the rotavirus vaccine and intussusception. Additives and preservatives such as thimerosal have also come under scrutiny. Because of thimerosal’s prevalence in childhood vaccines, concern has been raised about the potential for excessive mercury exposure in immunized children.<sup>11,12</sup>

In many instances the evidence for such associations is based upon case reports and observations of small populations.<sup>4,16,17</sup> These small datasets do not enable a researcher to distinguish between a relationship based upon chance or a relationship based upon causality. Further epidemiologic evaluation of larger populations is necessary in order to arrive at any definitive conclusion that the observations are not simply due to chance. In some instances—such as the withdrawal of the rotavirus vaccine—analysis of larger population-based data prompted the withdrawal action.<sup>21,22</sup>

What is clear is that because of the increasing complexity of vaccine science, more elaborate systems to monitor vaccine safety in large populations will be required. New combinations of antigens will complicate the task of correlating specific symptoms with individual vaccine antigens.

## Causality and Coincidence

The majority of reported adverse events do not present with clearly defined clinical or laboratory characteristics that allow for simple inferences on causality. Many diagnoses such as autism, chronic fatigue syndrome, seizures, diabetes and sudden infant death syndrome have multiple or unknown causes. The establishment of cause and effect requires a temporal relationship between the adverse event and the introduction of the postulated offending agent, confirmed via carefully designed epidemiologic studies, based upon the analysis of the frequency of the adverse event within a large population. Epidemiologic evidence can be categorized into several types of studies that vary considerably in their ability to attribute causality to a set of observations. Each of these types of studies are found in the public health and medical literature, with the carefully designed randomized clinical trials providing the greatest potential to differentiate cause from coincidence.<sup>4,16,17</sup> Causality, when it relates to rarely occurring events or diagnoses, demands studies of large populations.

Other types of studies, such as controlled observational and uncontrolled observational studies, are less reliable, while small case series do not provide a broad enough assessment of the risk for a rare event within a large population. Ultimately the goal of any study designed to establish causality is to attribute a specific clinical diagnosis to an event, confirm the association with laboratory data (e.g., the isolation of vaccine viral antigen), and to demonstrate that the adverse event is more common in the immunized population than a control group. With childhood immunizations, the majority of the population is immunized and a control group is difficult to define. Therefore, alternative analytical techniques are required to look at the timing of the adverse event and the incidence within large linked datasets such as large Health Maintenance Organizations (HMOs) and Medicaid.<sup>4,16</sup>

The majority of clinical symptoms and case reports<sup>4,16</sup> forwarded to the Vaccine Adverse Events Reporting System (VAERS) are of non-specific symptoms, thus complicating any analysis for causality. Because of this, new systems are being established to monitor large populations and undertake targeted investigations of specific reports submitted to VAERS. Additionally, a series of studies are required by the FDA prior to the licensure of any given vaccine in order to assess safety and efficacy. The continued evolution and improvement of this system is essential in order to assure vaccine safety and maintain public confidence.

## The System of Checks and Balances

### *Pre-Licensure Trials*

Prior to FDA licensure, vaccines are assessed for safety and efficacy. Initial tests are laboratory based and include animal studies. Following animal studies, phased human clinical trials are instituted in a scientifically rigorous design. Experimental design is blinded, randomized and has a placebo control. The assessment for common side effects is facilitated by the controlled design of these phased studies. Rare adverse events are more difficult to delineate during Phase I, II and III clinical trials because of the relatively small size of study groups. Phase I and II trials frequently enroll between 20 and 300 individuals. Phase III trials generally target larger groups of 1,000 to 3,000 although some recent trials with pneumococcal vaccine and live attenuated influenza have been larger (greater than 25,000). The relative risk to an immunized population for rare adverse events, or clinical diagnoses occurring less frequently than 1/1000 doses, cannot be determined from these small trials.

### *Post-Licensure Studies*

Post-licensure studies do not conform to the same scientific rigor of pre-licensure trials. Because they are largely observational assessments of vaccine safety, post-licensure data must be carefully analyzed due to the potential for bias and other confounding variables present because of the lack of control groups. Systems set up to evaluate post-licensure studies include passive surveillance systems such as VAERS, Phase IV Trials, Clinical Immunization Safety Assessment Centers and the use of large linked databases.

### *Vaccine Adverse Events Reporting System (VAERS)*

The VAERS system has been in place within the Department of Health and Human Services since 1990<sup>3,16</sup>; it is a collaboration between the Centers for Disease Control and Prevention (CDC) and the FDA. VAERS depends on observations and “case reports” submitted by clinicians or anyone else including parents. Reporting is encouraged and VAERS serves as a “sentinel” for changes in frequency of new or previously recognized adverse events. On average, over 10,000 reports are submitted annually to VAERS.<sup>16</sup> Twenty percent of reports are classified as serious—these include the categories of lethal/life-threatening, or causing disability or hospitalization.

VAERS role is to generate new potential hypotheses about causa-

tion of adverse events, not in confirming them. Health care providers are encouraged to report all significant clinical events temporally related to immunization without regard to the certainty that a vaccine was causally related to the adverse event. While the VAER's system can generate new questions more rigorous epidemiologic methodologies are required to determine causality. The recent observation of increased cases (and clustering) of intussusception after the introduction of the rotavirus vaccination is a case in point.<sup>21</sup>

#### *Clinical Immunization Safety Assessment Centers (CISA)*

Because of the observational nature of the data entered in the VAERS system the CDC is establishing a series of regional Clinical Immunization Safety Assessment Centers (CISA). CISAs serve as an additional level of scrutiny of selected patients whose symptoms or diagnoses may represent a new adverse event. The evaluation of cases is standardized and includes laboratory evaluations.<sup>4,16</sup>

#### *Vaccine Safety Datalink (VSD)*

The need for large population-based data in order to assess the likelihood of causality of rare events has led to the use of Phase IV surveillance studies (post marketing trials) and the establishment of the Vaccine Safety Datalink (VSD). Phase IV surveillance studies frequently have a sample size in excess of 100,000. The VSDs were first established in 1991 to evaluate the validity of rare associations by combining large-linked databases from several large HMO's. The VSD provides assessable data from a variety of sources, including immunization records, hospital discharge records, outpatient visits, and mortality data. Over 500,000 children (from birth to six years old, or 2 percent of the United States population in these age groups) have been studied through this methodology. Current plans are to expand VSD evaluation to all age groups.<sup>16</sup>

## The Evidence—Facts Versus Myths

### *Multiple Sclerosis and Immunization*

A series of case reports in the medical literature has raised concerns about the association between the onset of symptoms of multiple sclerosis (MS), and the timing of vaccination. In particular, studies have focused on the role of Hepatitis B vaccine in the onset of MS or the exacerbation of symptoms.<sup>23–27</sup> MS is believed to be an autoimmune disease characterized by destruction of the neuronal myelin sheath.

The safety of immunizing patients with multiple sclerosis has been studied utilizing a random controlled trial with influenza vaccine.<sup>28</sup> The results indicated no exacerbation of symptoms following immunization with influenza. A Netherlands study found that exacerbations of MS were higher after influenza illness suggesting that all patients with MS receive annual protection to influenza through immunization.<sup>29</sup> Confavreux and others, in a case-crossover study using subjects from the European Database for Multiple Sclerosis who had a relapse between 1993 and 1997, concluded that commonly administered vaccinations, specifically tetanus, hepatitis B and influenza, do not increase the risk of relapse in patients with MS.<sup>30</sup>

The results of a case-control study reported in the NEJM in 2001 in which the study population was two large cohorts of nurses in the United States concluded that there was no association between hepatitis B vaccination and the development of MS.<sup>27</sup> Several other studies in the United States that looked at large health claims databases, and a retrospective study in Canada, also failed to detect any association between Hepatitis B vaccine and MS.<sup>23,24,31</sup> The British Columbia study reviewed prevalence of MS before and after the implementation of an annual Hepatitis B vaccination program and found no difference in the pre and post vaccine rates.<sup>24</sup> Additionally, two studies, one utilizing the VSD project, should be completed and add to the volume of data in the near future. Finally, both the World Health Organization and the Viral Hepatitis Board have recommended no changes to the current immunization recommendations after review of the evidence.<sup>16,31</sup>

At present there is no clear evidence to support a causal link between MS and any immunization.<sup>23-26</sup> Existing case reports may represent temporal associations that are coincidental to the administration of vaccine. Several additional studies and trials have been concluded or are underway to further evaluate the potential for causality.

### *Type 1 Diabetes*

The cause of type 1 diabetes (formerly known as juvenile onset diabetes or insulin-dependent diabetes) diabetes is not known, but the disease manifestations and metabolic abnormalities result from the destruction of pancreatic  $\beta$ -cells, which normally secrete insulin. A variety of potential etiologic environmental and genetic factors have been studied to include immunizations. Analyses of the relationship of vaccinations to type 1 diabetes have found no causal link.<sup>32-35</sup>

Some studies have suggested that in animal models, vaccination given at birth may actually decrease the incidence of diabetes, while

vaccinations given later in life may cause an increased risk.<sup>36</sup> Similar data in humans is not forthcoming. A Swedish study in the mid-1980s demonstrated a decreased risk for type 1 diabetes after measles immunization and no correlation of disease with Bacille-Calmette-Guerin vaccine (BCG), smallpox, tetanus, pertussis, rubella or mumps vaccines.<sup>35</sup>

A retrospective study in Canada found no association between BCG and type 1 diabetes except that the vaccine may have contributed to a delay in onset of disease.<sup>37</sup> A large Finnish review of 100,000 children immunized with *Haemophilus influenzae* type b (Hib) vaccine revealed no increased risk of type 1 diabetes and no association between diabetes and the number of vaccinations administered.<sup>38</sup>

### *Lyme Disease Vaccine and Rheumatoid Arthritis*

With the licensure of the Lyme Disease vaccine, recent concern has surfaced about the possible association of this new vaccine and chronic arthritis. It has been postulated that in some post-vaccination patients a chronic Lyme arthritis may be more frequently seen after infection with *B. burgdorferi*, the cause of Lyme Disease. Researchers have hypothesized that an autoimmune reaction may follow and lead to chronic arthritis.

Evidence in the literature to support this hypothesis is lacking at present. During the initial pre-licensure trials, almost 11,000 patients were immunized, and occurrence of arthritis was not statistically different in the vaccine group versus the control group.<sup>39</sup> In the thirty-day post-vaccination period the report of adverse events remained similar in both groups. Because of the attention focused on this issue, post-licensure evaluation of the potential for association with arthritis continues.

### *Influenza and Guillain-Barré Syndrome*

Several neurologic syndromes have been temporally associated with influenza vaccine. These observations include rare findings of optic neuritis, brachial neuritis and cranial nerve palsies. The only statistically significant association between influenza vaccine and any neurologic diagnosis is with Guillain-Barré syndrome (GBS), and that association was seen only in the 1976 swine influenza vaccine.<sup>10,20</sup> GBS is a symmetrical ascending paralysis, usually reversible, which often presents as a sequel to several infectious diseases, typically one to six weeks post infection). Background incidence rates of GBS are 1-2 per 100,000.<sup>10</sup>

During the 1976-77 influenza vaccination campaign approximately 1300 cases of GBS were reported to the CDC, a vaccine associated risk of slightly less than 10 cases per million people vaccinated.<sup>3,10</sup>

Epidemiologic studies indicated that the rate of GBS exceeded that which would have been expected by 10 cases per million persons vaccinated. In subsequent years the relative risks were less significant ranging from 1.1 (1980-1988) to 3.0 in (1990-91). Significantly, outside of 1976, the risk for GBS in vaccinated individuals is no greater than one case (beyond what would be expected in an unimmunized population) of GBS per million persons vaccinated. This risk is significantly less than the risk of developing a severe complication from influenza infection itself.

### *MMR and Autism*

A great deal of public attention has recently focused on the suspected link between the MMR (mumps, measles and rubella vaccine) and autism.<sup>40</sup> Autism is a childhood developmental disorder characterized by impaired communication and social interactions, and repetitive activities that further restrict social interactions. It is estimated to occur in about 2/1000 children. To date there has been no causal link found between MMR and autism, and a recent large study of California children reported in the JAMA found no association.<sup>41,43,44</sup> In June 2000, the AAP convened a conference with parents, practitioners, and scientists to present information and research on MMR vaccine and autism, which concluded that the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders.<sup>45</sup>

Public awareness of this possible association appeared in 1998 following the publication of an article by A. J. Wakefield and others in the Lancet.<sup>46</sup> The study was derived from a case series of 12 patients who presented to a referral practice in England. The patients presented with a picture of inflammatory bowel disease and autism. An expert committee from the United Kingdom's Medical Research Council subsequently reviewed this report.<sup>16</sup> Significantly, the Council found no correlation between MMR and autism. The study was noted to have several limitations—it lacked a control group, and at least 4 of the 12 children demonstrated aberrant behavioral symptoms prior to the onset of bowel disease. In a subsequent study the same investigators failed to find the suspected causative agent (measles virus RNA) in patients with inflammatory bowel disease.<sup>42</sup>

A North Thames study published in *The Lancet* provided further clarification about the lack of a relationship between autism and the MMR vaccine.<sup>41</sup> The researchers showed that the rate of autism had been increasing since 1979 and there was no evidence of an increase in cases of autism after the introduction of the MMR vaccine in 1988. The

authors observed that the time of diagnosis with autism did not relate temporally to the timing of MMR vaccine administration, i.e. whether children were immunized prior to or after 18 months of age. And finally, the vaccine coverage rates in children with autism compared to that of the larger population were nearly identical, also refuting the assertion of an association between autism and vaccination.

Two additional studies—one in Sweden and another in California—found no causal link between MMR and autism.<sup>43,44</sup> The California study found no correlation between coverage rates for the MMR vaccine and autism rates.<sup>44</sup> Specifically, while coverage rates in California children increased and then plateaued, autism rates continued to climb. The authors commented that if a correlation existed one would expect that the rate of autism and coverage levels with MMR would parallel one another, and that this was not observed in the data they reviewed.

#### *MMR and Thrombocytopenia*

Thrombocytopenia (abnormally low platelet count) is associated with infection with wild-measles and rubella viruses.<sup>10,20</sup> The risk of thrombocytopenia is significantly greater in wild virus infections than the risk associated with vaccination. Thrombocytopenia is rarely associated with the MMR vaccine. Several reports indicate that the frequency of laboratory documented thrombocytopenia post-MMR vaccination ranges from 1 in 30,000 to 1 in 40,000. In the majority of cases the clinical course is benign.

#### *Rotavirus and Intussusception*

Rotavirus is one of the most common causes of severe diarrheal disease in the United States and is responsible for over 50,000 hospitalizations and 20 deaths annually. In August 1998 a tetravalent rhesus monkey-based vaccine was licensed. RotaShield, manufactured by Wyeth, was introduced as a three dose series for infants. During the next 9 months, 15 cases of intussusception (the telescoping of one segment of bowel into another resulting in obstruction) were reported to the VAERS system.<sup>21</sup> The majority of cases of intussusception (87 percent) followed the administration of the initial dose of vaccine.

While the frequency of observed cases of intussusception following vaccination with the RotaShield vaccine suggested an association, the overall number of cases within the population of children immunized remained small. Because of the preliminary status of the data and the relatively small numbers of cases and vaccinees, a statistically sig-

nificant risk attributable to immunization with the tetravalent rotavirus vaccine has not been reported.<sup>22,23,48</sup> A recent study by Chang and others demonstrated that the incidence of intussusception following the rotavirus vaccine is not clearly greater in the vaccinated versus the unvaccinated group. Chang's study also suggests that rotavirus vaccination may provoke intussusception in those who would have eventually developed intussusception within the first year of life.<sup>51</sup> However, the strength of the initial analysis in several states and VAERS prompted the Advisory Committee for Immunization Practices (ACIP) to withdraw its support for RotaShield on October 22, 1999. Ongoing analysis of large linked databases is continuing to track post-vaccine experience in those infants who received the vaccine.

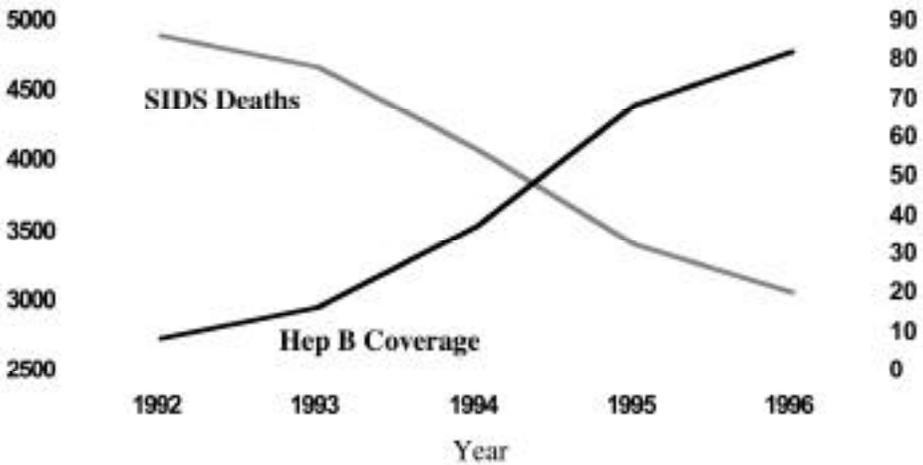
### *Thimerosal*

Thimerosal is a vaccine preservative which has been present in vaccines since the 1930's because of its antimicrobial activity. The antimicrobial action of thimerosal is particularly important where multi-dose vials are in use. A derivative of ethyl mercury, thimerosal contains approximately 49.6 percent mercury. Presently there is no evidence of that thimerosal has been causally linked to any health risk in children.<sup>11,12</sup> However, overall exposure of children to mercury is a public health concern and the removal of thimerosal from vaccines is a realistic measure designed to reduce total exposure to mercury.

In a thimerosal risk assessment conducted by the Food and Drug Administration (FDA) and reported by Ball and others, no evidence of harm other than local hypersensitivity reactions was demonstrated at doses of thimerosal found in vaccines.<sup>14</sup> However, Ball's report does suggest that some infants may be exposed to cumulative levels of mercury during the first six months of life that exceed Environmental Protection Agency (EPA) recommendations. In July 1999, based in part on the FDA's risk assessment, the AAP and the US Public Health Service issued a joint statement calling for the removal of thimerosal from vaccines.<sup>14</sup>

As a result of the desire to reduce mercury exposure, the AAFP, AAP and the ACIP established a goal in July of 1999 to remove or significantly reduce thimerosal in vaccines.<sup>12</sup> Manufacturers have responded to the concern. Both the Hepatitis B vaccine and the *Haemophilus influenzae* type b (Hib) vaccines are now available in thimerosal-free formulations. A thimerosal-free DTaP vaccine produced by Smith-Kline has been licensed in the United States since 1997. These changes have reduced exposure to ethyl mercury by at least 70 percent. It should be

Table 7: SIDS\* Deaths and Hepatitis B Vaccine Coverage in 19–35-Month-Old Children by Year of Survey, 1992–1996



\* U.S. residents, NCHS annual mortality files

noted that measles, mumps, rubella, varicella, inactivated polio and pneumococcal conjugate vaccines have never contained thimerosal. In addition, the CDC is utilizing its Vaccine Safety Datalink project to assess the potential of linkage between thimerosal-containing vaccines and several neurologic and developmental diagnoses.

Preliminary studies looking at very premature infants immunized with Hepatitis B vaccine containing thimerosal indicated the possibility of elevated mercury levels in those infants immunized during the first week of life. Similar studies in term infants failed to find blood mercury levels that exceeded background (less than 2 mcg/L).<sup>12</sup> Ongoing analysis of large linked databases is underway but preliminary analysis does not support a causal link between thimerosal and a variety of renal and neurologic diagnoses. Significantly, there was no increased risk detected in premature infants. Despite the decision to markedly reduce or remove thimerosal from the U.S. market, analysis of larger datasets is continuing.

*Hepatitis B Vaccine and the Reduction of SIDS Deaths*

Temporal associations between one event and another totally unrelated event can be confusing and a cursory look at data can result in erroneous conclusions. The number of deaths due to Sudden Infant Death Syndrome (SIDS) has dramatically declined since 1992. In 1992

there were just slightly less than 5,000 deaths attributable to SIDS annually. Over the ensuing four years, that figure fell by over 35 percent to approximately 3,000 deaths per year. Hepatitis B vaccine was introduced and coverage rates rose rapidly from less than 10 percent to over 80 percent during this same four-year period (see Table 7).

After analysis of this data, one could conclude that the introduction of the Hepatitis B vaccine and the subsequent rise in coverage rates correlated with the reduction in SIDS deaths. There is a temporal association between the two events but no causal link exists. Instead it is important to note that it was just prior to this time period that the medical community and the U.S. Public Health Service recommended that young infants be placed on their backs to sleep in order to reduce the risk of SIDS. It was this recommendation and not the rising coverage rates of Hepatitis B vaccine that resulted in the dramatic decline in SIDS deaths in the U.S.

### The Living Legacy of Vaccines

Significant and sustained progress has been made against vaccine-preventable diseases in the last century<sup>1,3,15</sup> (see Table 8). Prior to the implementation of routine immunizations, measles was responsible for a maximum estimated annual morbidity of 390,000 cases. In 2000 that figure was projected to be 81 cases of measles. Similarly, at its height, pertussis was responsible for almost 118,000 cases annually; this has been reduced to an estimated 6,031 in 2000. The percent change from maximum to current reported morbidity represents a decline of 97.63 percent for pertussis, and 100 percent in the case of polio. The worldwide impact of vaccines on preventable infections has also been impressive. The challenge to utilize this technology is an unremitting one as 11,000 infants are born daily in the United States alone, each needing a full series of immunizations.

#### *How Well Are We Doing?*

The national immunization effort has accomplished a number of goals within the last decade.<sup>1,3,15</sup> In 1998, and again in 1999, only one case of diphtheria was reported in the U.S. Polio has been eradicated in the Western Hemisphere and worldwide eradication is within sight. Certain national immunization goals for adults and children have been realized. For children between the ages of 19-35 months immunization coverage levels for the most critical initial doses of the primary series (DTP, Hib, polio and measles) reached the 90 percent level in 1996.

Table 8: Comparison of Maximum and Current Reported Morbidity, Vaccine-Preventable Diseases and Vaccine Adverse Events, United States, 1999

Disease	Maximum		1999*	Percentage Change
	Cases	(Year)		
Diphtheria	206,939	(1921)	1	-99.99
Measles	894,134	(1941)	86	-99.99
Mumps	152,209	(1968)	352	-99.76
Pertussis	265,269	(1934)	6,031	-97.63
Polio (wild)	21,269	(1952)	0	-100.00
Rubella	57,686	(1969)	238	-99.58
Cong. Rubella Synd.	20,000*	(1964–5)	3	-99.98
Tetanus	1,560*	(1948)	33	-97.88
Invasive HIB Disease	20,000*	(1984)	33	-99.83
<b>Total</b>	<b>1639,066</b>		<b>6,777</b>	<b>-99.58</b>
Vaccine Adverse Events	0*		11,827**	

Provisional totals of reported cases to the CDC.

\* Estimated because no national reporting existed in the prevaccine era.

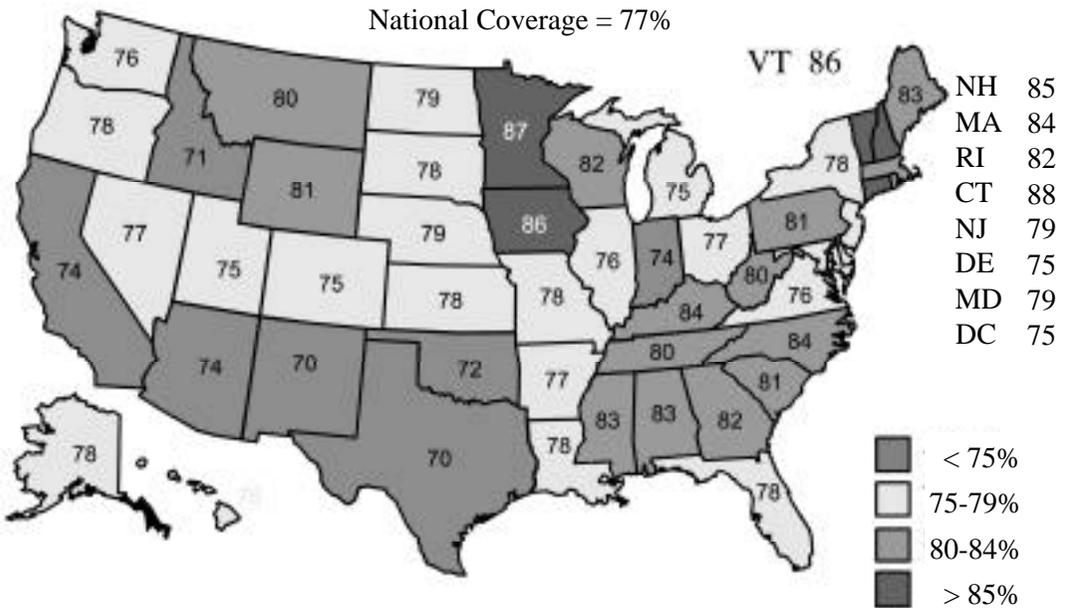
\*\* Adverse events after vaccines against diseases shown on table = 5,296

And presently 77 percent of 2 year olds nationwide have completed the full 4:3:1:3 series (4 DPT, 3 polio, 1 MMR, 3 Hib) in accordance with the recommended schedule (see Table 9). For adults the current national rate of coverage for the influenza vaccine in adults aged 65 and older was 63 percent, an increase from 58 percent in 1995.

### *The Measles Epidemic—The Wake-Up Call*

After over 57,000 cases of measles were reported in 1977, the Carter Administration targeted the interruption of measles transmission. In 1983 measles cases reached an all time low in the United States (1,497 cases). This success was not sustained and a resurgence occurred in older children and college-aged youth in 1984 and 1985. In 1986 a

Table 9: Estimated Vaccination Coverage with the 4:3:1:3 Series,\* by Coverage Level and State



\*4+DTP, 3+Polio, 1MMR, 3Hib

Source: National Immunization Survey, Third Quarter 1999–Second Quarter 2000

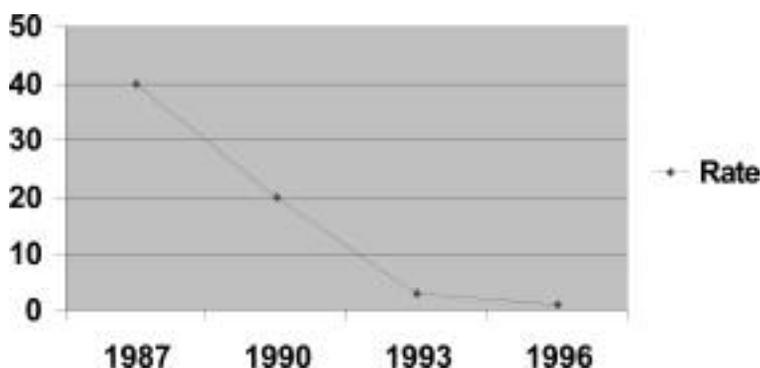
Children in the Third Quarter 1999–Second Quarter 2000 NIS were born between August 1996 and November 1998

different pattern of disease emerged as outbreaks were concentrated in preschool children, primarily those in low-income inner city settings.

These sporadic outbreaks through the mid to late 1980s became an epidemic in the three-year period from 1989 to 1991.<sup>3,49</sup> In the two-year period 1989–1990, over 43,000 cases and more than 100 deaths were attributable to measles. With the loss of community immunity and a large cohort of unimmunized and under-immunized pre-school children, the disease moved unabated through several major metropolitan areas including Chicago, Houston, Dallas and Los Angeles.

Analysis of the epidemic demonstrated that half of the children were not immunized, although a health care provider had seen the majority of them during the period of time in which they could have been immunized.<sup>49</sup> Children living in families that claimed a philosophical or religious exemption to measles immunization experienced a 35 fold increased risk for disease. These observations resulted in the con-

Table 10: Incidence\* of Invasive Hib Disease Among Children <5 Years of Age, 1987-1997



\*Rate per 100,000 children <5 years of age, estimated

cept of “missed opportunities.” Additionally, one in five of the unvaccinated children who contracted measles were enrolled in Medicaid, Aid for Families with Dependent Children (AFDC), of the Supplemental Nutrition Program for Women, Infants and Children (WIC). Several scientific reports of the epidemic ensued, describing the common attitude of complacency in the implementation of the national, state and local immunization policy of this country.<sup>49</sup>

The measles outbreak of 1989 to 1991 was a clarion call for sustained strategies designed to not only reduce morbidity and mortality but to maintain high levels of coverage. Periods of complacency in policy and action could lead to a resurgence of vaccine-preventable diseases.<sup>3,49,50</sup> This outbreak spawned a renewed federal and state effort in childhood immunization that resulted in the highest levels of vaccine coverage for children 19-35 months in 1999.

#### *The Potential—Haemophilus Influenzae Type b*

*Haemophilus influenzae* type b (Hib) is a highly invasive bacterium that is characterized by an age-dependent susceptibility. Hib disease attack rates peak around 7 months of age, and infections are uncommon after 5 years of age. Invasive diseases, or blood borne infections, characteristically become manifest as meningitis, epiglottitis, septic arthritis, and osteomyelitis. The mortality rate for Hib meningitis is 2–5 percent.<sup>10</sup> In the early 1980s active surveillance studies estimated that approximately 20,000 cases (40 to 50 per 100,000 children less than five years of age) of invasive *Haemophilus influenzae* type b occurred

nationwide. The rapid decline in the incidence of invasive *Haemophilus influenzae* type b after the introduction of the conjugate Hib vaccine is one of the most compelling success stories in modern immunization practice (see Table 10). The initial vaccine has been reformulated in order to increase its effectiveness in children less than 18 months of age. CDC surveillance studies reported only 144 confirmed cases of Hib invasive disease in the two-year period from 1996 to 1997.

### *Pockets of Need*

In the United States persistent disparities exist in childhood levels of immunization coverage. Coverage is a measure of the percentage of children immunized against vaccine-preventable diseases. After the measles outbreak of 1989 to 1991 the terminology “pockets of need” was coined to describe geographic areas of low vaccine coverage.<sup>49</sup> In 2000, state coverage levels for the 4:3:1:3 series ranged from 70 percent in Texas to 86 percent in Iowa, a slight decline in rate from the 1999 survey. It is estimated that approximately one million two years olds are missing one or more vaccinations.<sup>3</sup>

Overall the system in place to deliver immunizations has successfully reduced racial and ethnic disparities in childhood immunization levels, but coverage in areas of concentrated poverty remain substantially lower than nationwide averages. Recent nationwide surveys indicate a disparity of 9 percentage points between children living at or below the federal poverty level and those living above it.<sup>3</sup>

In many metropolitan areas the disparities in coverage are far more substantial. In certain inner city neighborhoods and low-income housing projects coverage levels are 20 percent lower than those reported in the county as a whole. Several recent inner city studies indicate that the national coverage data is not sensitive enough to detect variation of coverage within small areas. A targeted survey of poor children in Marion County, Indiana (Indianapolis) found the coverage rate to be 53 percent while the National Immunization Survey (NIS) reported a countywide rate of 78 percent. Similarly, a study of African-American children in Chicago found overall coverage rates of 36 percent and only 26 percent in public housing. The NIS reported a countywide rate of 59 percent in Cook County.

For adults, low coverage rates and significant racial and ethnic disparities continue to persist. Immunization coverage rates for adults are well below those achieved for childhood immunizations. Influenza coverage rates for adults over the age of 65 has increased to 63 percent, while levels of coverage for pneumococcal vaccine in this same age

group remain significantly lower at 42 percent.<sup>3</sup> More significantly for those individuals under 65 diagnosed with a chronic illness such as heart or lung disease the coverage rates are very low. Only 26 percent of those under 65 year of age with a chronic illness received the influenza vaccine and 13 percent received the pneumococcal vaccine.

There have been few targeted programs designed to vaccinate high-risk populations for hepatitis A and B for injection drug users or the children of migrant farm workers. Immunization rates for children with chronic illnesses such as asthma are even lower. Less than 10 percent of children with asthma receive the influenza vaccine. And to date there has not been the same level of concern for the implementation of nationwide adult immunization efforts for influenza and pneumococcal disease similar to those for the routine immunization of children.

### *Philosophical and Personal Exemption Policies*

A great deal of the success of early national immunization policy can be attributed to the implementation and enforcement of mandatory vaccination upon school entry. Recent research indicates that the implementation of philosophical and personal exemption policies at the state level have lowered coverage levels in children, thus creating a new definition of “pockets of need.”<sup>6-8</sup> Presently 48 states allow religious exemptions while 15 permit broader philosophical and personal exemptions.

Several recent published studies report an increased risk for preventable infections in populations where these policies are in place. Two studies, one in Colorado and another in California, place the increased risk for contracting measles at 22.2 to 35 times greater for children whose parents exempt out of mandatory school entry immunizations (exemptors).<sup>7,8</sup> The Colorado study by D. Feikin and others demonstrated the increased vulnerability of underimmunized communities to pertussis and measles as a result of the adoption of a personal exemption policy.<sup>7</sup> Significantly, schools with pertussis outbreaks were identified to have more exemptors and the presence of exemptors increases the risk for vaccine-preventable disease for all children.

The timing of the measles outbreak of 1989–91 may have been affected by philosophical and personal exemptions.<sup>8</sup> In a review of the California data, timing of the measles outbreak may have been accelerated by one year in exemptors. International studies reinforce the finding of increased risk for disease in countries with low coverage rates in part attributable to philosophical or personal exemptions.<sup>6</sup> Pertussis rates were 10 to 100 greater in countries with lower coverage rates as a result

of active anti-vaccine movements. Polio has been introduced on several occasions into North America by exponents previously residing in Western Europe.<sup>10</sup> Increased surveillance of the impact of expanded exemption policies is needed in order to assess the impact on coverage rates and changes in disease burden within groups of individual exponents and the risk transmitted to entire communities.

*Vaccines: A Good Investment*

Immunization has consistently been found to be one of the most cost effective and health effective interventions in our modern medical arsenal.<sup>1,15</sup> The role of vaccines will increase as new technologies enable practitioners to prevent (not just treat) an expanded variety of infectious agents and perhaps chronic illnesses. The return on investment for vaccination is substantial. Vaccines reduce preventable morbidity and mortality while saving health care and business related expenditures. For example, the CDC has demonstrated that vaccines reduce time lost from work and school (indirect savings). Lower rates of coverage can result in an increase in health costs and lower productivity for the business sector.

The CDC has analyzed both direct medical savings and indirect savings for most major childhood vaccines (see Table 11). The returns on investment for direct medical savings vary from 50 cents on the dollar for infants immunized for Hepatitis B to over ten dollars for MMR.

Table 11: Benefit-Cost Analysis of Commonly Used Vaccines (Savings per Dollar Invested)

Vaccine	Direct Medical Savings	Direct + Indirect*
DTaP	\$8.5	\$24
MMR	\$10.3**	\$13.5**
H. Influenzae type b	\$1.4	\$2.2
Hepatitis B-		
Perinatal	\$1.3	\$14.5
Infant	\$0.5	\$3.1
Adolescent	\$0.5	\$2.2
Varicella	\$3.03	\$5.4
All IPV	\$0.9	\$5.45

\* Indirect savings includes work loss, death and disability

\*\* Recently revised to include 2nd dose MMR

Direct plus indirect savings vary from approximately two dollars returned for every dollar invested for *Haemophilus influenzae* type b to over 24 dollars for DTaP. The cost of the vaccine in most cases is significantly less than the cost of one 10-day course of a third generation cephalosporin. These costs are in addition to the costs of human suffering.

### Summary: Vaccination Good—Disease Bad

Our nation's progress toward eradicating vaccine-preventable disease provides a revealing insight into the workings of the American health care system and, more specifically, the priorities of both the federal and state governments. The reduction of the burden of infectious disease in adults and children represents one of the nation's greatest health achievements in the latter half of the 20<sup>th</sup> century. Despite advances in science, only one disease—smallpox—has succumbed globally to our public health efforts utilizing modern immunization practice. Although progress has been substantial in the reduction of vaccine-preventable disease over the last two decades, periodic incursion by microbes have resulted in several major outbreaks in the United States.

Nationally, coverage rates for children are at or near an all-time high; however, coverage rates in certain regions of the country and large metropolitan areas remain low. In 1998, statewide coverage levels for 2-year olds for the 4:3:1:3 series varied widely, from 71–90.4 percent (79 percent average nationwide). Subsequent analysis of the 1999 data demonstrated a slight decline in statewide coverage rates ranging from 70 percent to 86 percent, with an overall nationwide rate of 77 percent. Furthermore, children below the poverty level are less likely to be fully immunized than children above that level.

Following the measles resurgence of 1989 to 1991, the National Vaccine Advisory Committee (NVAC) concluded that despite advances in vaccine development, complacency combined with fragmented delivery and under financed systems contributed to increased rates of disease morbidity and mortality. Missed opportunities, disjointed state and federal programs for children, and an inability to track and verify immunization coverage in both private medical practices and public health clinics were cited as contributing factors in the measles outbreaks.

The science of vaccine development is as dynamic as the evolving health care system and the methodologies to measure the impact of their effectiveness. The number of vaccines in widespread use is projected to grow from 11 in 2000 to over three times that number in 2020.<sup>3</sup> The

nation's commitment to improving coverage levels and eliminating vaccine-preventable diseases faces challenges on numerous fronts. These include: the incorporation of new antigens and antigen combinations into the vaccine schedule; the need to immunize a new cohort of approximately 4 million children annually or 11,000 newborns a day; immigration and international travel; migrant workers; concerns about vaccine safety and vaccine related diseases; and the evolution of microbial resistance to new antibiotics.

Viruses and bacteria, however, do not suffer from these burdens and challenges and unfortunately adapt all too readily to therapeutic advances. Antibiotic resistance in a variety of bacteria is accelerating. The role of vaccines is paramount in the struggle to combat evolving resistant microbes. The effectiveness of the pneumococcal vaccine in the backdrop of increasing rates of penicillin resistance (25–85 percent) is but one example. Coverage rates, although at or near an all-time high, are not sufficient to protect this nation from periodic epidemics. Recent policy trends designed to exempt more individuals from immunization may have the unintended consequence of increasing the risk of outbreaks in both those who exempt out of mandatory immunizations and those who live, work or attend school in these same communities.

As health care costs continue to escalate and the population ages, prevention must become an increasingly important and accepted strategy. Vaccines sit atop the pinnacle of preventive health care. Their full potential is yet to be realized.

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## Glossary

**Active Vaccine:** a major category of vaccines that stimulate the host's immune system to produce specific antibodies or cellular immune responses or both, which protect against or eliminate a disease (p. 881).

**Autism:** a complex developmental disability resulting from a neurological disorder that affects the functioning of the brain; impacts the normal development of the brain in the areas of social interaction and communication skills; typically appears during the first three years of life.

**Auto-immune disorders:** a condition in which the immune system mistakes self tissues for non-self tissues and mounts an inappropriate attack; examples of autoimmune diseases include multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis.

**Guillan-Barre Syndrome:** an inflammatory disorder of the peripheral nerves (those outside the brain and spinal cord) characterized by the rapid onset of weakness and often, paralysis of the legs, arms, breathing muscles and face; also called acute inflammatory demyelinating polyneuropathy or Landry's ascending paralysis; most people recover but it can take months and may result in varying degrees of long term disability.

**Hepatitis B:** infection caused by the hepatitis B virus (HBV), which attacks the liver; virus is transmitted through blood and body fluids that contain blood; HBV is the world's most common serious liver disease and is 100 times more infectious than the AIDS virus.

**Herd immunity:** indirect protection from disease resulting from a high enough proportion of the population being immunized thus interrupting the transmission of disease in the community.

**Idiopathic Thrombocytopenia Purpura:** a bleeding disorder caused by a low blood platelet count, (the clotting factor in blood); occurs when a patient (adult or child) forms antibodies which destroy his or her own platelets; typically a patient's platelet count is less than 20,000-30,000 upon diagnosis, whereas the lower limit of the normal range is 150,000.

**Intussusception:** telescoping or prolapse of one portion of the bowel into an immediately adjacent segment; most commonly occurs at the terminal ileum.

**Multiple Sclerosis:** chronic, often disabling disease of the central nervous system; occurs when the protective, insulating coating around the axons called myelin, comes under attack by the body's immune system; symptoms may be mild such as numbness in the limbs or severe, such as paralysis or loss of vision; most people are diagnosed between the ages of 20 and 40 and the unpredictable physical and emotional effects can be lifelong.

**Passive Vaccine:** a major category of vaccines consisting of a preparation of antibodies that neutralizes a pathogen and is administered before or around the time of known or potential exposure (p. 881).

**Species Variant Vaccine:** a type of vaccine in which an animal virus that causes a veterinary disease similar to a human disease is isolated and cultivated, the anticipated outcome is that the animal virus will be attenuated for humans yet will be sufficiently related immunologically to the natural human virus to elicit protective immunity to the human agent.

**Type I Diabetes Mellitus:** chronic disease which generally occurs in young, lean patients and is characterized by the marked inability of the pancreas to secrete insulin because of autoimmune destruction of the pancreatic beta cells; patients are dependent on exogenous insulin to sustain their lives; requires long-term medical management both to limit the development of its devastating complications and to manage complications when they do occur.

**Variolation:** inoculation into the skin of healthy people material from smallpox pustules or scabs from infected patients in order to protect against smallpox.

**Attenuation in Cell Culture:** a vaccine production strategy in which the wild-type virus isolated from a natural human infection is passed in vitro through one or more cell types that the virus ordinarily does not encounter in vivo with the goal of attenuating its pathogenicity (p.885).

**Reassorted genomes:** are derived after coinfection of a culture with two different viruses with segmented genomes contains genes from both parental viruses (p.885).

**Temperature Sensitive Mutants:** viruses that are selected according to their growth properties at different temperatures, the idea behind this approach is that the temperature-sensitive virus will be less vigorous in their in-vivo growth than their wild-type parental virus, thus less viru-

lent and phenotypically attenuated. (p.885).

**Adjuvant:** vaccine additive designed to enhance the immune response to vaccines; aluminum salts are currently the only adjuvant licenses for human use, vaccine antigen binds stably to the aluminum salt by ionic interactions and forms a macroscopic suspension in solution.

**Lypholized:** form of vaccine storage in which the vaccine is freeze dried and is resuspended in diluent at the time of administration (p.881).

**Stabilizers:** vaccine additive used to extend the shelf-life or dating-period for the vaccine.

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