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Michael D. Scheiber

To ADA and the start of our new life together
MDS

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ACKNOWLEDGEMENTS

INTRODUCTION

Vaccine-related injury epidemiology and litigation are currently "hot" topics at both the state and national level. In November of 1986, the President signed an act to establish a national fund to provide compensation and medical care necessary as the result of severe adverse reactions to required immunizations. This act acknowledges that there exists necessary but inherently dangerous products for which no-fault remedies are appropriate. Enactment of the federal legislation has great symbolic importance, but has little immediate practical importance since it awaits Congressional funding.

The solution to the problems surrounding adverse reactions to vaccination events still has several missing pieces. It is unclear how many misadventures really are associated with various vaccines and if anything can be done to reduce the number of injuries. Also, the current reporting systems of both California and the national Centers for Disease Control need to be assessed to determine how well these systems reflect the true occurrence of misadventures. In order to predict the magnitude of order of the problem, current immunization levels in California and the systems which measure such levels must also be assessed.

This paper addresses these issues and makes policy recommendations based on findings from vaccine data. A brief history of immunization is provided as background material, and

adverse reactions to pertussis immunizations are examined in some detail. Finally, the policy environment in which immunization takes place is traced from the eighteenth century to the present time.

Chapter One

A HISTORY OF IMMUNIZATION

Variolation: Ancient Attempts at Disease Prevention

The eradication of smallpox from the world demonstrated both the potential and the reality of effective modern vaccination programs. Yet, for many centuries before the development of international vaccine programs, it was recognized that a cause and effect relationship existed between certain agents and disease, and early attempts at protection from these diseases can be found in historical records. This chapter traces the development of immunization practices from ancient times to modern programs.

Mithridates, the mythological King of Pontus, is said to have protected himself against poisons by drinking the blood of ducks that had been treated with them. Pliny the Elder believed that the livers of mad dogs could cure people with rabies (1).

There is evidence that the ancient Egyptians placed snake venom in open scratches on their skin (2), and as early as 590 B.C. the Chinese were implanting bamboo splinters dipped in the pustules of natives ill with "tai-tou" (smallpox) into the nasal mucosa of susceptibles (3). Chinese doctors would also dry and pulverize smallpox scabs and blow them into the noses of healthy susceptibles, or smear pus and lymph from draining smallpox pustules on the

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1. Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 1-2.

2. Joklik WK, Willett HP, Amos DB, eds. Zinsser microbiology. 18th ed. Norwalk: Appleton-Century-Crofts, 1984: 6.

3. Fulginiti V. Immunization in clinical practice. Philadelphia: J.P. Lipincott Company, 1982: 1.

inside of children's nightshirts and make the children sleep in them (4).

These early methods of inoculation with live smallpox material are collectively termed variolation. Variolation against smallpox is no longer practiced today and, as will be discussed in this chapter, has been replaced by vaccination, a slightly different process. While the protection against natural infection by the smallpox virus is the goal of both methods, vaccination, rather than using actual smallpox material, uses vaccinia virus (i.e. cowpox) as the immunogen. Both methods are types of immunization practices.

Chinese variolation practices spread throughout Asia via trade routes and were well-accepted in the Middle East. In Russia, smallpox lymph was spread onto the branches used for post-sauna massages, and variolation was accomplished through steam-opened pores.

Such practices must have been founded on the knowledge that certain diseases such as smallpox, when they did not result in death, conferred lifetime protection in the individual against subsequent disease. However, the historical context of these early attempts at immunization must be emphasized. Variolation was not removed from the contemporary pre-Enlightenment explanatory social paradigms, and, far from following scientific standards, was often shrouded in spiritual, magical, and religious ceremony.

Furthermore, there were two major drawbacks to variolation. The first was that the desired case of smallpox which was

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4.   Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 42.

deliberately acquired was occasionally fulminant enough to prove fatal. The second major drawback, which made variolation both imprudent and impractical unless recently inoculated patients could be isolated, was the fact that the inoculees were contagious and could spread full-blown smallpox to any susceptible contacts.

Although variolation was apparently already being widely practiced in other parts of the world for twenty centuries, C.W. Dixon, in his excellent history of smallpox (5), traces the first smallpox inoculations in the Western World to England in the eighteenth century. The Lady Mary Wortley Montagu is generally cited as being largely responsible for the introduction of the practice. As the wife of the British ambassador to Turkey in 1716, she wrote in her personal correspondences of seeing thousands of Turkish children "ingrafted" by the passage of pustulent material from the lesions of smallpox victims into their open veins. She reported that the children would develop a fever for only two to three days and that during that time they displayed amazingly few pox lesions. One objective of variolation practices in Turkey at a time when "from smallpox and love few remain[ed] free" is thought to have been the preservation of beauty for the harems; unmarked female Circassian slaves who had been inoculated as infants commanded extremely high prices (6).

5.   Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962.

6.   Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 21-2.

As evidence of the previously mentioned spiritual significance attached to this process, it is interesting to note that Lady Montagu related how the "superstitious Grecians" practiced variolation in the shape of the cross, opening veins at the forehead, both arms, and the chest. Since Lady Montagu, who had lost a brother to the smallpox and had suffered a mild case herself, had heard no reports of death caused by the inoculations, she expressed her intent to try it on her own son (7). Upon the family's return to London in April of 1721, her daughter became the first person to be professionally inoculated in England. The procedure was performed by Dr. Charles Maitland, who had acted as surgeon to the embassy in Turkey during Lady Montagu's stay.

In June of 1721, with the permission of King George I, Maitland began a series of experiments with inoculation on condemned prisoners in Newgate Prison in exchange for the granting of pardons. Although the trial group contained only six prisoners, the experiment met with such success that the Princesses Amelia and Caroline were soon after variolized (8). This is also one of the first recorded examples of incarcerated human subjects being employed by practitioners of Western medicine during the development of medicinal regimens.

Variolation became prevalent in England. The usual technique was to bandage a thread that had been dipped in fresh smallpox material and then dried into an area of scarification on the patient's

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7.   Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 219.

8.   Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 223

skin. Despite the success enjoyed by the practice in England, variolation was slow to spread to the rest of Europe. First reports of inoculations in Holland are found in 1749, in Germany in 1750, and in France in 1755. Inoculation was not practiced in Spain until 1770.

However, perhaps as the result of close British ties, inoculation was first practiced in Colonial America as early as 1721. The Boston Gazette reported that

> "Dr. Walter Harris, a Fellow of the College of Physicians, entertained that learned Society on April 17, 1721 with a very judicious discourse. He takes notice that... a most innocent and safe way of inoculating the Small Pox found out among the unlearned Orientals, was now by the good providence of God brought unto us... so we may have the Small Pox after a safe and easy manner, in that method, if God please graciously to smile upon it. And it arrives unto us the more seasonably because the Small Pox of late hath made fearful destruction among people of higher as well as lower quality among us: whereas the inoculation, duly managed... forever preserves and wonderously defends people from suffering that sort of Small Pox which has proved to be so dangerous" (9).

Not only did the Colonies enjoy the dispersion of information from Britain, but the African slaves that were being shipped to the Colonies brought with them the knowledge of traditional African variolation practices. Cotton Mather, of witch-hunting fame, owned slaves and had learned of variolation from them. When a slaveship brought with its cargo enough cases of smallpox to cause the abovementioned frightening epidemic in Boston, Mather persuaded Zabdiel Boylston, a local physician, to try the African method of

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9.   The Boston Gazette. Mon. Jan. 29 - Mon. Feb. 5, 1721.

inoculation on two of Mather's own slaves, his six-year-old son, and several other healthy Bostonians. However, news of the severity of the cases and the deaths caused by these early inoculations caused Virginia and several other of the colonies to outlaw the practice (10). And by the order of the Select Men of Boston, those he had treated who were "under Inoculation for the Small Pox were removed to Spectacle Island, on Tuesday last, 4 or 5 Days after they had undergone the Operation and before they were sick therewith. Doctor Zabdiel Boylston... at a Publik Town-Meeting... did solemnly promise to Inoculate no more without the knowledge & appreciation of the Authority of the Town" (11).

In fact, in Colonial America where post-inoculation isolation procedures were not always carefully followed, a number of epidemics, the worst of which was in 1752 and claimed over five hundred Bostonians, have been traced to inoculations. While, as will be discussed in later chapters, data surrounding adverse reactions to immunizations is difficult to collect accurately even today, some figures do exist for Colonial America. In 1721 only two percent of the smallpox cases in Boston were traceable to inoculations. But as the practice spread in the cities this proportion increased to twenty-eight percent in 1752 and eighty-seven percent in 1764 (12). These figures demonstrate an interesting fact about early immunization

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10.   Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 43.

11.   The Boston Gazette, Mon. May 14 - Mon. May 21, 1722.

12.   Rothstein WG. American physicians in the 19th century. Baltimore: Johns Hopkins University Press, 1972: 31.

practices: extremely high rates of adverse and even fatal reactions to immunization were frequently encountered. The fact that the use of immunization became widespread despite this fact suggests an interesting hypothesis.

Within a modern paradigm the scientific community readily accepts stastistical measurements delineating the risks and benefits associated with certain activities and medical procedures. It is possible that 18th century populations had similar notions of risk and benefits, albeit without the statistical reasoning, and that the willingness of populations to accept the risks associated with immunization reflected a rational decision-making process. Smallpox was a common disease, epidemics of which frequently decimated whole populations. Because the disease was so dreaded, people were willing to accept a very high risk of injury from the immunization practice. Alternatively, however, it seems possible that these people did not have a good grasp of the risks involved with inoculation, and that the process which we would refer to as cost-benefit analysis did not enter into their thinking. If it had, it would seem likely that the spread of variolation would not have been so readily accepted in Europe and the Colonial United States.

However, the driving force behind these early attempts at disease prevention was often powered by more than simply benign, humane desires. A recurring theme in the development of vaccination is the desire for national power. Before the advent of effective weaponry, the balances of many wars were tipped by the health of the respective armies. The American Revolution was no exception. The Colonial troops invading Canada suffered such heavy

casualties from smallpox that Thursfield would write that smallpox was "the main cause of the preservation of Canada to the British Empire" (13). Encouraged by Benjamin Franklin, who had lost a son from smallpox, and publicly declaring that smallpox was "more destructive to an army in the natural way than the sword" (14), George Washington ordered the variolation of the entire Colonial Army in 1777 at the expense of one death per three hundred soldiers inoculated by the live virus. Despite Lady Montagu's claims, Chase writes of early variolation practices that "Historically, variolation was only too often deadlier than the average smallpox infection." The famous mathematician Daniel Bernoulli estimated that sixty million deaths occurred from smallpox in Europe alone during the eighteenth century. However, it should be noted that almost seventy-five percent of those who contracted the disease did manage to survive, albeit scarred and often blinded (15).

Jenner and the Development of Modern Vaccination

European and British folklore from the eighteenth century indicates that the cows in certain geographical regions often suffered a pustulent disease of the udder. Due to the similarity of the resultant lesions to human smallpox, this disease came to be known as cowpox. It was also known that the handling of these udders by

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13. Thursfield. Smallpox in the American war of independence. Ann Med Hist 1940; 2: 312.

14. Rothstein WG. American physicians in the 19th century. Baltimore: Johns Hopkins University Press, 1972: 31.

15. Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 42-83.

dairy workers could cause the appearance of cowpox lesions on the hands. While it may have be noted in numerous other parts of Europe and Britain, the dairy farmers and civil leaders in Gloucestershire, England took particular notice of the fact that those milkmaids who had suffered from cowpox seemed to contract smallpox with a much lower frequency than did the general population. Furthermore, when they did suffer from smallpox, their illnesses were less severe and rarely fatal (16). Dixon suggests that the beauty of dairymaids extolled by local folklore was due in part to their unpock-marked faces from what is now known to be cross-protection from the cowpox virus.

Although there is some controversy as to whether or not Benjamin Jesty, a prominent Gloucestershire cattle trader, was the first to experiment with using cowpox material to deliberately inoculate his family, this practice and the first experiments surrounding its use are generally attributed to Doctor Edward Jenner, a physician and scientist in Berkeley, Gloucestershire. Jenner had good personal reason to desire the development of a practice to replace variolation, for in 1757, as the eight-year-old son of a wealthy and influential man, Jenner, along with his other boarding school classmates, was subjected to variolation.

Jenner recalled this process to his biographer Baron (17). "There was bleeding till the blood was thin; purging till the body was

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16. Southey C and LR. The life of Bell. London: 1844.

17. Baron J. The life of Edward Jenner...with illustrations of his doctrines and selections from his correspondence. London: H. Colburn, 1827.

wasted to a skeleton; and starving on a vegetable diet to keep it so. For six weeks I was bled and purged, kept on a low diet, dosed with medicine, and was then removed to one of the so-called 'inoculation stables' and haltered up with others in a terrible state of disease." The inoculation was performed by the local apothecary Mr. Holbrow by opening up the skin on the arms of the boys with a knife tip and then bandaging smallpox scabs into the open wounds. While such elaborate ordeals may not have been common in other parts of the world or even Europe, Jenner's experience was evidently fairly typical of upper class British variolation methods.

Having suffered through this ordeal, Jenner was more than receptive to the local folklore delineating the decreased smallpox attack rate among milkmaids who had been previously exposed to cowpox. He also learned that some farmers deliberately handled infected cow udders in an effort to protect themselves from smallpox. In fact, Jenner was so enthusiastic about the possibility of discovering a prevention for smallpox, that the local medical society threatened to expel him if he did not stop discussing the subject of cowpox at society meetings.

On May 14, 1796, Jenner, convinced that he would be successful, inoculated James Phipps, a local eight year-old boy, with pus from a cowpox lesion on the hand of a dairymaid. Jenner then challenged the boy seven weeks later by inoculating him with smallpox material. Phipps remained healthy, and thus was born the practice of vaccination, a word derived from *vaccinia* (L. relating to cows), and a process developed before the description or isolation of

viruses. Today, the virus responsible for cowpox which provides cross-protection against smallpox is known as the vaccinia virus.

Vaccination quickly replaced variolation as a public health measure in Europe since adverse reactions tended to be milder than those to variolation and the vaccinated subject was not contagious to others (18). This delighted Jenner who corresponded with Jean de Carro, a physician in Vienna who started vaccinating his patients in 1799 with lymph received from Jenner. "Conscious of its [vaccination] importance," Jenner wrote, "it was always my hope that the subject would be taken up on the Continent, and I am much gratified to see it fall into such able hands in Vienna; for I never had a fear of its failure but from its being conducted by those who were incapable of making just discriminations" (19). Dr. de Carro used his influence to help spread the practice through Austria, Hungary, Poland, and part of Germany.

Vaccination began slightly later in France, delayed by war and revolution. But in 1800 a French translation of Jenner's vaccination pamphlet sold out three editions in only seven months (20). In an 1802 correspondence with a Parisian surgeon, Jenner wrote that "I have the happiness to tell you that the pretty general introduction of the Vaccine in our Metropolis has already manifestly diminish'd the

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18. Kimball JW. Introduction to immunology. New York: Macmillan Publishing Co., Inc., 1983: 7.

19. Miller G, ed. Letters of Edward Jenner. Baltimore: Johns Hopkins University Press, 1983: 9-10.

20. Drewitt FD. The life of Edward Jenner. New York: Longmans, Green, & Co., 1931: 60.

number of Victims to the Casual Smallpox. I trust the Metropolis of France can boast of similar gratification" (21).

Spain soon adopted the practice of vaccination which had been introduced via Paris. In 1803, under the King's orders, an expedition was sent throughout Spain's colonies in both the Old and the New Worlds to diffuse vaccination. Jenner was elected a member of the Royal Economical Society of Madrid, and it was declared of his work that "There is no country likely to receive more benefit from your labours than Spain... for the inoculation for the cow-pox has been received with the same enthusiasm here as in the rest of Europe." This expedition successfully introduced the practice to China and South America (22).

Jenner became an international hero and a man of great influence. When two Englishmen were being detained in France, then at war with Britain, Jenner wrote to the Committee of Vaccination in Paris for their release. The Committee suggested that Jenner should write directly to Napoleon, which he did. Napoleon, who reportedly replied "Jenner! Ah, we can refuse nothing to that man," released the prisoners (23).

Following the publication of Jenner's pamphlet in 1798, several American physicians, led by Benjamin Waterhouse of Boston,

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21. Miller G, ed. Letters of Edward Jenner. Baltimore: Johns Hopkins University Press, 1983: 10-17.

22. Drewitt FD. The life of Edward Jenner. New York: Longmans, Green, & Co., 1931: 60-62.

23. Drewitt FD. The life of Edward Jenner. New York: Longmans, Green, & Co., 1931: 79.

introduced the new practice of vaccination to the United States. Cowpox was unknown in America at that time, so the physicians imported a supply of cowpox lymphatic material from England. By 1802, vaccination was being practiced in all the major ports as well as some inland areas such as Mississippi, Kentucky, and Ohio (24). In that same year, vaccination became publicly supported in New York, marking the first public vaccine program in the United States.

A volunteer association was established to provide free vaccination for the poor, and the city appropriated $200 annually for the vaccination of the indigent population. Since that time, publicly supported immunization programs have become one of the mainstays of public health efforts, both in the United States and internationally. Later, President Jefferson, his family, and his neighbors were all successfully vaccinated, lending further credit to the practice (25). Jefferson, who performed many vaccinations himself, wrote somewhat prophetically to Jenner in 1806 that "Future generations will know by history only that the loathsome smallpox existed and by you has been extirpated" (26).

Human experimentation to determine the adequacy of protection was not confined to Europe. William Osler, one of history's most famous physicians, reported that in 1802 in a Boston

24. Rothstein WG. American physicians in the 19th century. Baltimore: Johns Hopkins University Press, 1972: 31.

25. Drewitt FD. The life of Edward Jenner. New York: Longmans, Green, & Co., 1931: 59.

26. Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 27-8.

experiment, nineteen boys were vaccinated with the cowpox. Three months later, twelve of them were inoculated with smallpox with no resultant disease. As a control, two unvaccinated boys were inoculated with the same smallpox virus; both of these unfortunate subjects contracted the disease. As conclusive evidence of the fact that "cowpox is a complete security against the smallpox," Osler noted that the nineteen vaccinated boys were again challenged, this time with live smallpox virus from the two controls, again without contracting the disease.

Rothstein points out, however, that the practice of vaccination spread quickly in the United States without a consequent advance in the medical science of vaccination. The exact manner of using the vaccine had not yet been worked out and pure vaccine was not always used, so sporadic groups of vaccinees would become sick from the vaccinations or would not acquire immunity. Also, even Jenner himself had no idea why the vaccine worked, as the modern concept of the immune system was still many decades away from being worked out. In fact, Jenner's earliest ideas about the cowpox were wrong. He felt certain that the disease came from horses. In a letter to Mr. Edward Bevan in 1798, two years after his first successful vaccination, Jenner wrote that "...this tends to strengthen what I so strongly suspect that the disease arises from morbid matter generated by a horse" (27).

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27. Miller G, ed. Letters of Edward Jenner. Baltimore: Johns Hopkins University Press, 1983: 9.

Therefore, Rothstein attributes the spread of the practice to two reasons. First, it was similar to variolation, so it was not a shockingly new concept to the people. Second, despite scattered failures, it was repeatedly and more or less consistently shown that cowpox vaccination did indeed provide protection against the dreaded smallpox.

It is interesting to contemplate the reaction of the medical community if an effort were made today to introduce the widespread use of a new practice that was founded on such uncertain grounds. While its basis was logical within the framework of Jenner's contemporary scientific paradigm, the legitimacy of his vaccine was based, it seems, on the success of a large-scale natural human experiment.

Pasteur and the Rabies Vaccine

Since that time, the history of the development of modern vaccines is full of successes, failures, and anecdotal evidence. Fulginiti writes that "Vaccination became a medical, political, religious, ethical, and social phenomenon, often simultaneously. Not until the advent of modern biological knowledge did the procedure and its descendants [sic] assume a more balanced place in human history" (28). In fact, in a more lengthy discussion of the topic, each of these viewpoints (medical, political, etc.) would constitute a

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28. Fulginiti V. Immunization in clinical practice. Philadelphia: J.P. Lipincott Company, 1982: 2.

different but interesting lens through which to view the development of modern vaccination practices.

Any of these lenses, however, would have to stop and focus on Louis Pasteur who, as he does in so many other aspects of science, occupies an important place in the history of the development of vaccines. He was perhaps the first to suspect that the protective response provided by bacterial vaccines was not necessarily related to the entire micro-organism. He suggested that the response might be "directed against certain of their constituents or products." His first vaccines were for animals, developing the chicken cholera vaccine almost by accident in 1877 when he noticed by chance after a two weeks' vacation that old cultures of the bacillus did not produce the typically lethal disease in experimental animals. His heat-attenuated anthrax vaccine for sheep was first used in 1881.

When Pasteur was nine years old in his native village of Arbois, a rabid wolf had infected eight people. Pasteur witnessed the cauterization with a hot iron of one man's wound. Some fifty years later, in 1885, Pasteur made the most important breakthrough ever in the treatment of rabies in humans. Without recognizing the viral agent, he made a rabies vaccine from the dried spinal cords of infected animals. Building on his prior experiments with attenuated rabies viruses in dogs, he recognized that the noninfectious material he obtained from heating the spinal cords could still be used as an effective vaccine antigen.

Counting on the long time span in humans between an animal bite and central nervous system disorder, Pasteur successfully prevented the fatal consequences of natural infection by immunizing

a patient, nine-year-old Joseph Meister, immediately after he had been bitten by a rabid animal. The rabies virus was finally isolated as a transmissible agent in the early years of this century, but for many years Pasteur's process was used essentially unchanged to protect those who had been bitten by rabid animals and those who worked in high-risk fields from the terrors of rabies.

The Development of Heat-Killed Vaccines: Typhoid and DTP

Building on Pasteur's concepts, Daniel Salmon and Theobald Smith in the USDA laboratories in Washington, D.C. developed a vaccine made from the remains of Hog cholera bacilli heat-killed at 56' C to protect livestock from the Schweine-pest in 1886. They showed that their heat-killed preparation protected pigeons against repeated doses of virulent *Salmonella* that were high enough to kill unvaccinated pigeons. In the process, they proved to the scientific world that not only attenuated micro-organisms but killed micro-organisms could be used for effective vaccine production.

Smith, whose family had changed their name from Schmidt after immigrating from Germany in 1848, ironically chose medicine only as a second choice when he failed to get a job as a teacher after graduating from Cornell University (29). Other of Smith's many accomplishments included the first proof that infection could pass in

29. Zinsser H. Biographical memoir of Theobald Smith, 1859-1934. Presented to the National Academy of Sciences at the annual meeting, 1936. In: National Academy of Sciences of the United States of America: Biographical memoirs, vol. XVII. Washington, D.C.: National Academy of Sciences, 1937: 262-303.

ticks from mother to offspring, important knowledge today in preventing the transmission of several of the Rickettsial diseases, such as Rocky Mountain spotted fever.

Smith's work also extended into the treatment of diphtheria, as he described improved methods of effectively producing diphtheria antitoxin in horses. In the early 1890's, Emil A. von Behring in Berlin used such an antitoxin to immunize human subjects with a fair amount of success. His contemporary, Rudolf Virchow, now commonly known as the "Father of Pathology," was both an important political and scientific figure. Virchow was a proponent of this antitoxin and "referred to the surprisingly good results obtained in the Emperor Frederick Hospital. He said it was the duty of every physician to use the serum despite the injurious effects that might result from it. He thought years would pass before the value of the serum could be fixed definitely" (30).

Despite the fact that Shibasaburo Kitasato, a Japanese postdoctoral graduate working in Berlin, had isolated the diphtheria toxin in 1890, passive immunity as conferred by the antitoxin was the method used to prevent the morbidity and mortality associated with diphtheria well into the twentieth century, when the toxoid was attenuated and used to provide active immunity. Kitasato also later isolated the tetanus bacillus and proved that it was the etiological agent responsible for "lockjaw."

Building on the methods of Salmon and Smith during that same decade, Pfieffer and Cole used heat-killed typhoid bacteria as an

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30. The New York Herald, Dec. 5, 1894.

immunizing agent for the first time in 1896. Almrath Wright improved upon their technology and developed a successful typhoid vaccine by 1898, which proved to be one of the most effective military "weapons" of the turn of the century. In 1898 nearly 35,000 people in the U.S. died of typhoid. Seven times as many soldiers died from typhoid than from battle wounds in the Spanish-American War. 1,125,000 British troops were immunized against typhoid during World War I, among whom 7,500 cases and 266 deaths occurred, a mortality rate of 0.236/1000. During the South African War, however, 73,633 unimmunized soldiers contracted typhoid, 10,144 of whom died (31).

The development of a successful technology for the manufacture of heat-killed vaccines paved the road towards an efficacious pertussis vaccine. In 1906 Jules Bordet and Octave Gengou grew *Bordetella pertussis* in artificial medium for the first time, and researchers in many different parts of the world began work on a heat-killed pertussis vaccine (32). Louis Sauer of Northwestern Medical School, Charles Nicolle at the Pasteur Institute in Tunis in 1913, and Thorvald Madsen in Denmark in 1914 all developed cellular pertussis vaccines that met with varying success. After World War II Pearl Kendrick, a member of the Michigan State Health Department, combined her pertussis vaccine with the altered

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31. Fulginiti V. Immunization in clinical practice. Philadelphia: J.P. Lipincott Company, 1982: 3.

32. Joklik WK, Willett HP, Amos DB, eds. Zinsser microbiology. 18th ed. Norwalk: Appleton-Century-Crofts, 1984: 519.

toxins of diphtheria and tetanus to produce the first DTP vaccine (33).

Influenza, Gonorrhea, and Meningitis Vaccines

In the terrible influenza pandemic in 1918-1919, more than twenty million people around the world lost their lives to what was then mistakenly considered to be a disease caused by *Haemophilus influenzae*. Smith and his co-workers did not manage to isolate the true virus until 1933. An effective vaccine was not developed until 1943 when the Army demonstrated a seventy-five percent protection rate from an influenza vaccine made from formalin-inactivated influenza viruses.

Pasteur's concept of protective components was not wasted on Wolfgang Casper. During the 1920's and 1930's he was a pioneer in working on the development of capsular polysaccharide vaccines against both pneumococcal pneumonia and gonorrhea. In 1927 Casper and Oscar Schiemann published the results of an experiment that indicated that the injection of these purified components protected mice against pneumonia caused by the specific strains of pneumococci from which the polysaccharides had been isolated. These results caused quite a commotion in the scientific world. Since these chemical components were germ-free, vaccines using such antigens had the distinct advantage over more traditional vaccines

33. Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 243-5.

that they were entirely incapable of causing pneumonia or any other disease.

By 1930, he had also purified capsular components from the bacterium *Neisseria gonorrhoeae* and had prepared a vaccine against gonorrhea. However, since man is the only known susceptible host to gonorrhea, an animal model was not available and human experimentation was called for. He used ten healthy men and one woman (a prostitute who was being treated in his hospital for gonorrhea) in his experiment in Berlin. Five of the men were vaccinated and the remaining five acted as the control group. All ten had intercourse with the prostitute, with four of the control group contracting the disease. None of the five vaccinees contracted the disease from the infected prostitute. However, in the midst of a world depression, no drug company was willing to take the great economic risk of proving the worthiness of Casper's vaccine, and so no large-scale testing was ever performed (34).

With World War II came the widespread use and rapid development of effective antibiotics. Allan Chase writes of this period that "The old dream, nearly two centuries old by now, of preventing all infectious diseases by vaccination, rather than merely curing them, was all but killed by the... impact of the sulfas and antibiotics on nearly every bacterial... disease known to humankind" (35).

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34.   Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 23-26.

35.   Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 36.

Casper and his wife, both Jewish, had escaped Hitler in 1935 and come to America. He was placed in charge of the gonorrhea division of the U.S. Public Health Service during the war, but the need to return gonorrheic soldiers quickly to the front placed the emphasis of gonorrhea research and treatment on the new wonder drugs. Vaccine development was at the bottom of the list, and the effectiveness of the antibiotics against gonorrhea, as well as a host of social and economic factors both in this country and developing countries has made the possibility of widespread vaccination against gonorrhea unlikely at best, even today.

Just as military prowess had provided the impetus to develop an effective typhoid vaccine at the turn of the century and had squashed Casper's hopes of developing a gonorrhea vaccine, a renaissance of interest in vaccination may have grown out of the desire in the 1960's to establish a healthy U.S. Army. The armed services had routinely been using sulfa drugs to protect its recruits from *Neisseria meningitidis*, the bacterium that causes epidemic meningococcal meningitis. As more and more drugs were used, more and more resistant strains developed until "it became increasingly evident that the sulfa drugs could no longer be used to protect crowded training camps against outbreaks of the disease" (36). A team of Army researchers at Walter Reed made speedy progress and by 1968 had produced a safe and effective vaccine against meningococcal meningitis. Mass trials were performed in 1973 in army recruits, and in American children in 1974. During 1975, the

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36. Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 37.

majority of the populations of Finland and of Brazil were immunized against different types of meningococci, both public health efforts being credited with the prevention of huge epidemics.

The Polio Vaccine Story

No history of vaccination, no matter how brief, would be complete without some discussion of the development of the poliomyelitis vaccines (37). These vaccines, despite a dubious start, have virtually been able to eliminate from our society one of the most dreaded and tragic diseases of humankind.

Work on a polio vaccine probably began in 1910 when Paul Römer made up a heat-inactivated vaccine. However, some of the monkeys in his study contracted paralytic polio so this vaccine was abandoned for fear of similar results in human subjects. He later developed a formaldehyde-inactivated vaccine which was also abandoned when it failed to provide protection to the mice in his experimental population. His early failures illustrate a phenomenon that was present throughout the development of the first vaccines, but marked a change from the acceptance of variolation practices. Before the use of modern statistical analysis and sample size calculation, one failure could scuttle many attempts at the development of effective vaccines. This may represent a changing conception of risk from the early Colonial times when, as discussed, fatalities and failures were much more widely accepted. It may also

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37. mainly derived from Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 280-304.

reflect changing social norms and the new emphasis that had been placed on the role of scientific proof and demonstrable fact by the Progressives.

More promising work was accomplished in 1931 when Maurice Brodie published an article on the active immunization of monkeys against poliomyelitis. William Park, who was instrumental in the development of the diphtheria antitoxin, brought Brodie to New York to work with him in the New York City Health Department Laboratories. By July of 1934 Brodie and Park had developed a formalin-inactivated vaccine which they tested on themselves for safety, and then on a half-dozen volunteers at NYU-Bellevue, where both Albert Sabin and Jonas Salk were starting their medical careers.

After testing the new vaccine on themselves, their colleagues, and twenty monkeys, the Park-Brodie vaccine was declared safe, and the newspapers reported that it posed no danger. Within days, John Kolmer in Philadelphia independently announced that he had developed a live attenuated polio vaccine that had been tested successfully on forty-two monkeys, himself, his children, and twenty-two other children. All three insisted that there was only one type of polio virus. It was later discovered that all three were wrong.

By the summer of 1935, 10,000 children in various parts of the country had been given the Park-Brodie vaccine, and 12,000 children had been given Kolmer's vaccine. But later that year, James Leake of the U.S. Public Health Service reported that twelve people who had been vaccinated with either formula had developed paralytic poliomyelitis, and six had died. Further studies showed that the

Park-Brodie vaccine provided only very low titers of antibodies in monkeys, and that large doses of the Kolmer vaccine induced paralytic polio in monkeys. In November of 1935, both vaccines were removed from the market and destroyed. Kolmer, at a meeting of the American Public Health Association, is reported to have stood and said, "Gentlemen, this is one time I wish the floor would open up and swallow me."

It is possible that these two vaccines did not confer immunity, and it is possible that they may actually have caused some or all of the twelve polio cases. But with new knowledge about the causative agent of paralytic polio came the possibility that these vaccines had been perfectly safe and effective against Type I polio virus, and that the cases were caused by strains of the rarer Types II or III viruses. A huge collaborative report headed by the National Foundation for Infantile Paralysis (the March of Dimes) reached the conclusion in 1951 that there were three types of polio virus. Sabin and Salk both had important positions in this effort.

Salk developed a formalin-inactivated vaccine against all three types (trivalent) and began careful testing in human subjects in 1952. In 1953 mass testing began. By April of 1955, 400,000 doses had been administered to the nation's children when chaos arose. Doses from seven improperly inactivated lots manufactured by Cutter Laboratories in Berkeley, California were causing active cases of paralytic polio and even death. Once these lots were removed and destroyed, the hysteria surrounding the matter slowly abated and confidence in the vaccine was regained, aided by the fact that the

Canadian government had administered 860,000 doses without a single case of paralytic polio among the vacinees.

Despite the huge success of the Salk vaccine, protection was not complete, and minor epidemics like the one in 1959 provided the impetus for an effort to develop a live attenuated poliovirus vaccine. After the earlier complications encountered with human subjects testing, the idea of mass testing the trivalent oral live attenuated polio vaccine that Sabin eventually developed was not well-received in the United States, so the majority of testing was done abroad. Having proven its safety and effectiveness in Sweden, Czechoslovakia, and the U.S.S.R., the vaccine was finally licensed for production and use in the United States in March of 1962.

Today debate continues over which polio vaccine should be used routinely. The live oral polio vaccine provides greater protection from prodromal and gastrointestinal illness caused by the polio virus than does the inactivated vaccine. However, the latter has been associated with a lower rate of poliomyelitis in otherwise healthy vaccinees, their contacts, and immunocompromised recipients.

Other Live Virus Vaccines: The Development of MMR

Coincident with the acceptance of mass polio immunization was the widespread adoption of a vaccine for measles for the first time. As early as 1758, Francis Home, a Scottish physician, successfully inoculated several subjects by scarification with blood taken from infected patients. Not only did he provide measles immunity in these people, but he also proved the transmissibility of the disease

(38). The type of variolation from pustules that was done for smallpox could not be done for measles since the typical measle vesicles do not contain copious amounts of pustulent material the way smallpox lesions do. Physicians in Europe, however, aware of the possibilities of transmitting syphilis and TB by smallpox variolation, were unwilling to submit their patients to the greater risk involved with bloodletting to prevent measles, generally a milder disease.

Nearly two centuries later in 1938, Harry Plotz grew the measles virus in chick-embryo cultures at the Pasteur Institue. Researchers at the Rockefeller Institute built on this technology and developed an experimental vaccine that was used to immunize a few dozen people, including some children, in 1941. During the War, the Army did a fair amount of work with egg-passaged and attenuated live virus vaccines, but efforts were abandoned due to the severity of reactions in healthy recruits (39).

Finally in 1960, Enders developed a live virus vaccine that was tested in increasingly larger groups of children. The vaccine was further attenuated by Schwartz and licensed in 1963. From 1963 to 1967 an inactivated measles vaccine was also available in the United States, but was removed from the market when it was discovered that a large number of children were developing a severe, unusual illness following immunization. In 1973, the CDC issued a report

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38.   Joklik WK, Willett HP, Amos DB, eds. Zinsser microbiology. 18th ed. Norwalk: Appleton-Century-Crofts, 1984: 1061

39.   Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 310-312.

stating that 24 million cases of measles had been prevented in the first ten years of measles vaccination, representing an economic savings of $1.3 billion.

The acceptance of measles vaccine occurred right in the middle of the worst rubella epidemic in United States history in 1963-1964. The resultant incidence of congenital rubella syndrome in this country set vaccine developers to work, and by 1966, Paul Parkman, Harry Meyer, and Theodore Panos had developed a live attenuated rubella vaccine.

Slightly earlier, during the War, Enders had developed an inactivated mumps vaccine. By 1965 a live attenuated vaccine was being tested in Philadephia, and by 1968 a variant had been licensed for general distribution. Today, in developed countries, measles, mumps, and rubella are usually combined and given as the MMR vaccine series starting at around 15 months of age.

Vaccines: A Modality of Unfulfilled Promise?

In addition to preventing countless numbers of cases of infectious diseases, the pursuit of new vaccines has greatly broadened our scientific information base. Fulginiti points out that much of our present knowledge about immunity and the immune system is the result of work done while developing vaccines. He attributes the discovery of cell mediated immunity to Koch during his search for a vaccine against tuberculosis and the discovery of passive immunity to von Behring and Kitasato in their work with diphtheria antitoxin.

In the middle of this century, Enders and Wellers discovered that poliovirus could be cultured in non-nervous tissue in primates other than man, a discovery that made the advancement of the polio vaccine possible, and in 1961 Hayflick and Moorehead grew human diploid fetal cells *in vitro*, a technique which is used today to culture inactivated rabies, live oral polio, and live rubella virus vaccines.

Yet, despite the development and control of several vaccine-preventable illnesses in this country, the promise of safe and effective vaccine technology has not had the impact in the last century that one might have expected. Diphtheria and measles kill many children in developing countries, and our own population is inadequately immunized against these preventable diseases. Chase writes that, "Historically... vaccines... have yet to live up to the multiple potentials of induced immunizations that became apparent when smallpox variolation was supplanted by safe and effective, cross-reacting live cowpox virus vaccine. Only about a dozen really useful vaccines against bacterial and viral diseases have been developed and put into general use in the nearly two centuries since Jenner" (40).

This chapter has shown that the history of inoculation and induced immunity is a long one that began in ancient times with variolation procedures, the spread of which encompassed most of the globe. Edward Jenner's late eighteenth century work has to be credited as the single most important breakthrough in vaccine

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40.   Chase A. Magic shots. New York: Wm. Morrow & Co., 1982: 468.

technology and has allowed for the eradication and control of several epidemic infectious diseases.

Testing of vaccines was performed on human subjects until the early part of this century, but has largely been abandoned in recent years until the very final stages of vaccine trials. These trials are discussed in a later chapter. Also, with the advent of modern scientific procedures and statistical methods, vaccines that are not one hundred percent effective are much less likely to be discounted than were earlier experimental vaccines after small failures. Federal licensing procedures have helped to provide gold standards of acceptable risk and efficacy to which the early pioneers did not have reference.

The development of the "wonder drugs," or antibiotics, has also played an immeasurably important role in decreasing mortality from bacterial infectious diseases. In some sense their success seems to have guided the emphasis of vaccine research towards the viral illnesses, against which we have far fewer effective drugs. Successful technology has also brought the development of vaccines to a full circle. The injection of live virus preparations with the resulting risks of fulminant disease in recipients or disease transmission to contacts is not far removed from the ancient practice of variolation.

Today, the development of vaccine technology continues, as virus fractionation, ultracentrifugation, genetic reassortment, and recombinant DNA techniques allow for the production of safer and more effective vaccines. Pasteur's concept of immunogenic subunits is the underlying theory behind much of modern vaccine research, a

fact as discussed in a later chapter is evidenced by the recent development of the acellular pertussis vaccine in Japan.

It should be noted that the potential of vaccine utilization may yet come to fruition in this century. Smallpox vaccine eradicated the threat of mortality from a disease that throughout history has decimated entire populations. Today we are faced with another epidemic that was insidious in its start but is now a world-wide problem, the death toll of which could potentially surpass that from smallpox. The employment of all the vaccine technology and other scientific breakthroughs that have been made since Jenner's time to develop a safe and successful vaccine against the Human Immunodeficiency Virus, the etiologic agent of AIDS, would represent one of the most significant breakthroughs in modern medical and social history.

Chapter Two

IMMUNIZATION LEVELS IN CALIFORNIA

Introduction: Preventable Diseases Still Plague California

Ever since Edward Jenner's work in the late 1700's with cowpox vaccines, long before an understanding of the immune response had been worked out, vaccination and immunization programs have taken on increasingly important social, public health, and medical roles. In 1977 a Federal effort was made to increase immunization levels in the United States. In that year the National Childhood Immunization Initiative was announced by then Secretary of Health, Education, and Welfare Joseph Califano and presented this country with a goal of raising immunization levels in American children for the common vaccine-preventable diseases to over 90% by 1979. This goal was achieved with success in school age children, and two new goals for 1990 were established in December of 1980 by the U.S. Public Health Service: 1) to raise national immunization levels in toddlers to 90% by age two, and 2) to raise the immunization levels of children in day care centers and schools (grades K-12) to 95%.

In California in 1977, Senate Bill 942 was passed into law and provided a comprehensive compulsory school immunization law that took effect in 1978. Fig. 2.1 (compiled from CDHS data) compares the morbidity of selected vaccine-preventable diseases in California for 1977 and 1985 and demonstrates that considerable progress has been made in decreasing the incidence of these diseases.
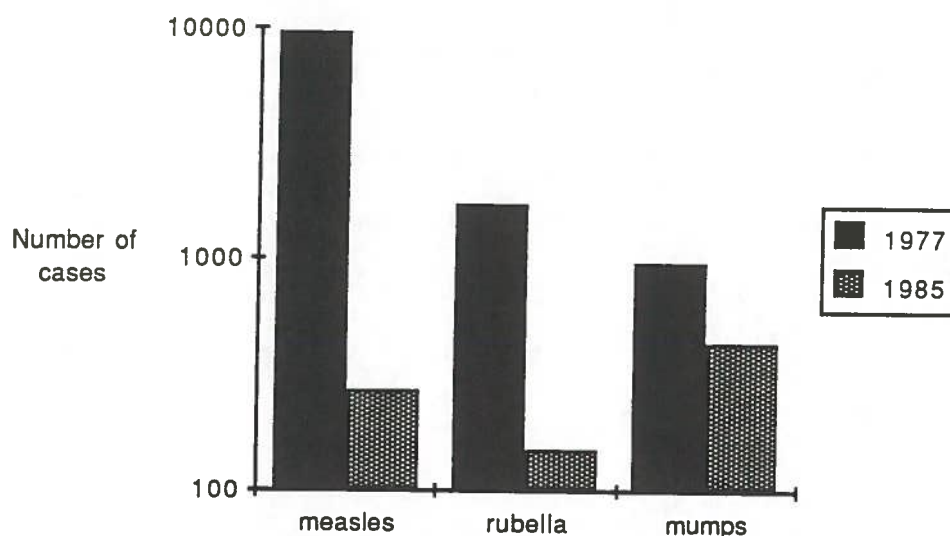
Fig. 2.1. Number of cases of selected vaccine -preventable illnesses in California in 1977 and 1985 (compiled from CDHS data).

Yet in the time span 1978-June 30, 1986 over 17,000 cases of vaccine-preventable infectious diseases were reported in the state of California alone (41). During the period July 1985 - June 1986, 37.0% of the measles cases in California were classified as preventable. In 1982 and 1983 for the nation as a whole, 68% of reported pertussis cases in children 3 months to 6 years of age occurred in inadequately immunized children (42). National estimates indicate that susceptibility rates to measles or rubella may be as high as 20% in our colleges and universities (43). There were major measles outbreaks in California in Los Angeles County in 1984, Riverside County in 1985, and San Bernadino and Sonoma counties in 1986.

David White and Frank Fenner write that "Fear is the principal

41.   data from CDHS

42.   Centers for Disease Control. Pertussis: United States, 1982 and 1983. MMWR 1984; 33: 573-5.

43.   data from CDHS

factor motivating people to seek or accept immunization for themselves and their children. Even in the case of a dreaded disease such as polio, it is difficult to maintain enthusiasm for a program of universal immunization after the disease has become very rare" (44). Yet the children of this country should enjoy continued protection from easily preventable diseases.

Objectives

It is therefore essential from the public health standpoint to carefully examine current immunization levels and assess recent trends in levels over time. It is also important to uncover factors that may contribute to fluctuations in immunization levels. The exploration of these parameters is the objective of this chapter which will include: 1) a presentation and discussion of immunization levels in California school children and recent policy changes undertaken to improve these levels; 2) a description of the method by which the state gathers immunization status data; 3) age-grouped data which illustrate that certain segments of children in this country are underimmunized and at increased risk for the contraction of preventable infectious diseases; and, finally, 4) a discussion of some of the weaknesses of the current surveillance system.

Immunization Levels in California School Children

The kindergarten survey completed on 1/22/87 by the

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44. White D, Fenner F. Medical virology. 3rd ed. London: Academic Press, Inc, 1986: 299.

California State Department of Health Services' (CDHS) Immunization Unit shows that, in 1986, 90.12% of all children beginning kindergarten (public and private schools combined) in California had school records indicating that they had received all the immunizations required for school registration (see Appendix One for California vaccine requirements). Fig. 2.2 demonstrates that, over the past several years, the percentage of children who are adequately immunized at the start of kindergarten has increased about 15% since 1979.

Fig. 2.2. The percentage of students entering kindergarten in Calif. meeting all vaccine requirements at the time of school entry by year from 1979 to 1986 (compiled from CDHS data).

In general, however, the state of California falls slightly below the national weighted average that the Centers for Disease Control (CDC) report for the percentage of children entering kindergarten that have fulfilled state requirements for all immunizations (Fig. 2.3).
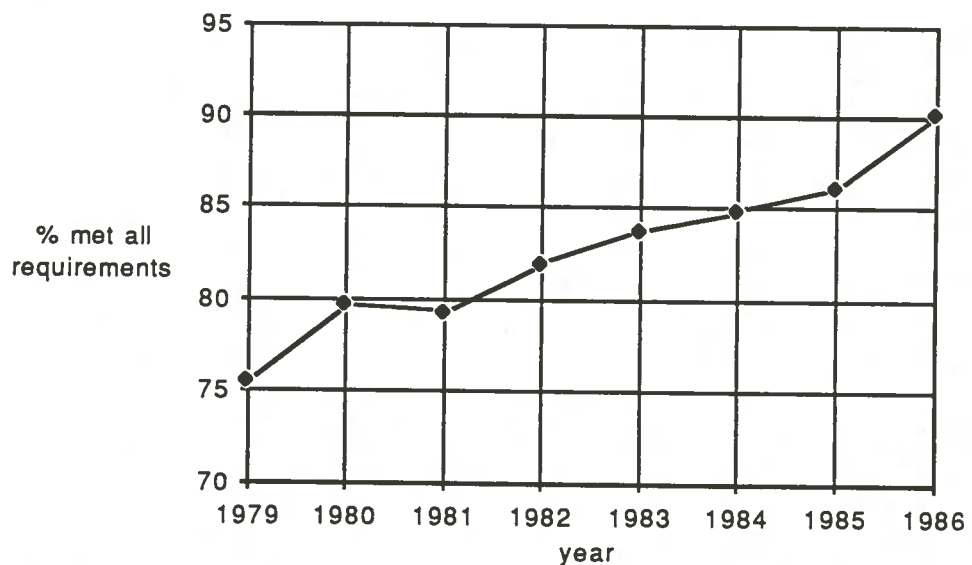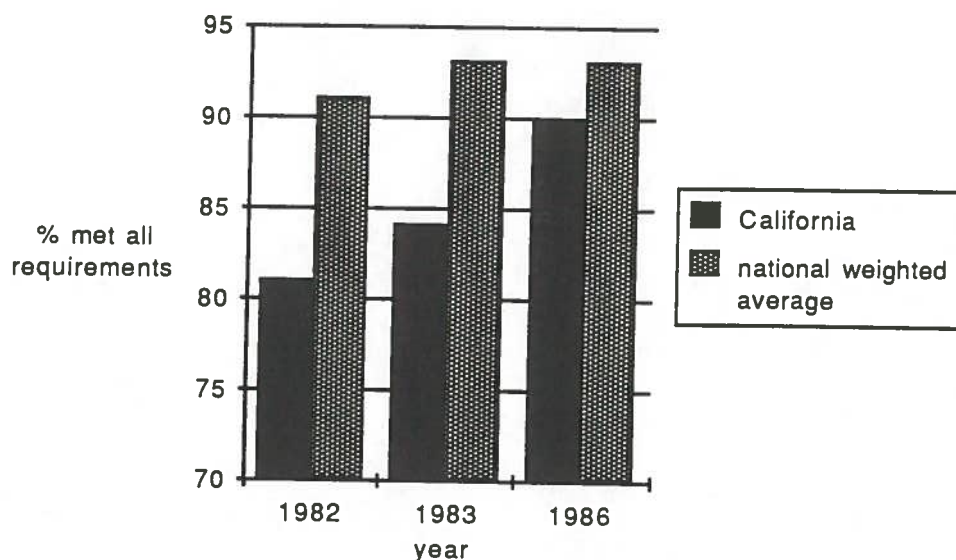
Fig. 2.3. Percentage of students entering kindergarten in Calif. meeting all vaccine requirements at time of school entry compared to the national weighted avg. by year from 1982 to 1986 (compiled from CDHS and CDC data).

Immunization Levels: Monitoring and Surveillance Methods

The Immunization Unit of the CDHS conducts extensive annual surveys known as selective reviews to carefully review and establish the validity of data about the immunization status of children in California's schools and child care centers. The purpose of the reviews, as outlined by the Immunization Unit, is to evaluate the effectiveness of follow-up of conditionally admitted students, to verify the data obtained on the annual Kindergarten Assessment (school entry data), and to conduct retrospective studies of immunization levels of children at various age checkpoints. Since the initial school review in 1981, the state has added a similar review of child care centers (45).

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45. The CDHS defines a day care center as any facility located outside of a private home, usually with more than 12 children, and does not confine its data collection to only those institutions licensed by the Dept. of Social

The kindergarten surveys were performed on a voluntary basis between 1974 and 1977 and were made mandatory by Senate Bill 942 after 1978. The new law requires that one employee from each school with a kindergarten compile all the California School Immunization Records (CSIRs-- see Appendix Two) for the kindergarten children and tally the numbers and percentages of children up-to-date for each of the required vaccinations. These totals are forwarded through county health departments to the Immunization Unit of the CDHS in Berkeley.

The selective reviews are generally conducted at just under 300 schools in California. Before starting the selective review process, the CDHS determined that just over 280 schools needed to be sampled in order to achieve 95% confidence intervals that would allow the estimation of the percentage of unimmunized children to be in the range of 10%. For example, if the level of unimmunized children was determined by the selective review to be 15%, then the 95% confidence interval would range from 10% to 20%. It should be noted, however, that the schools at which selective reviews are performed are not chosen by an entirely random process. A school is selected at random by a computer, but if that school has already participated in a previous selective review, it is replaced into the sampling pool and another school is selected at random. The CDHS has accepted the small loss in validity generated by this selection system because it is outweighed by the increase in quality control of record-keeping that generally results from a school's participation in

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Services.

a selective review.

Two children at each school are selected at random from a random numbers table and their CSIR's are reviewed by CDHS staff members. Two studies were performed, one in Los Angeles County and the other at the state level, which measured the accuracy of the CSIR as compared to home records (those immunization records which parents had in their possession). Both studies indicated that, when parents had kept written immunization records, they matched comparably with the CSIR's within a margin of 5% error. The retrospective aspect of the selective review studies allows the state to identify underimmunized portions of the population to be targeted by policy and other methods aimed at improving immunization levels.

Recent California Statute Changes Aimed at Increasing Immunization Levels in Children

The selective review process also allows the state to analyze the impact of legislation aimed at improving the immunization level of California's children. When Senate Bill 942 was enacted in California in 1977, much of the confusion surrounding vaccine requirements for school registration was clarified and uniform requirements were instituted. Historically, separate immunization laws were enacted for individual vaccine-preventable diseases in California. These laws were unclear as to who was responsible for determining whether or not a pupil had received the required immunizations. Furthermore, there were no specific policies regarding the exclusion of students who wished to attend schools but

were not fully immunized. Senate Bill 942 repealed these existing immunization laws and substituted one uniform law for all specified immunizations. It also standardized school immunization records, entrance requirements, and sanctions against unimmunized students. More recently, additional procedures have been implemented to augment the school entry laws. On March 5, 1986, two principal changes went into effect.

The primary change requires children entering California schools or child care centers for the first time to provide a written immunization record for each required vaccine dose (or a written exemption from the requirements). This written record from a health care professional must include at least the year and month of vaccine administration. Prior to this change, guardians without written immunization records for their children had the option of filling out and signing the California School Immunization Record. This change was made in an effort to eliminate the "creation" of a less-than-accurate school record between well-meaning parents and helpful school officials.

The second change was the abolition of the ten-day grace period for new pupils. Previously, pupils new to the California school system who were missing one or more currently due vaccine doses were allowed to attend classes for a grace period of ten school days. During this time period, the child's parent or guardian was responsible for having all required doses administered to his child. Now all currently due vaccine doses must be received and verified with a written immunization record before school entry.

School Compliance with Official Policy

As would be expected for California as a whole, as immunization levels rise, the total percentage of students with conditional admissions to kindergarten (those needing one or more immunizations who were allowed to attend classes for the grace period) has been declining (Fig. 2.4). The 1987 Selective Review indicated that 85% of public kindergartens and 75% of private kindergartens were strictly and completely enforcing the new school entry regulations at the time of the survey. In the day care centers, the new regulations were being enforced by 88.5% of Head Start Programs, 74.3% of public day care centers, and 64.1% of private DCC's.
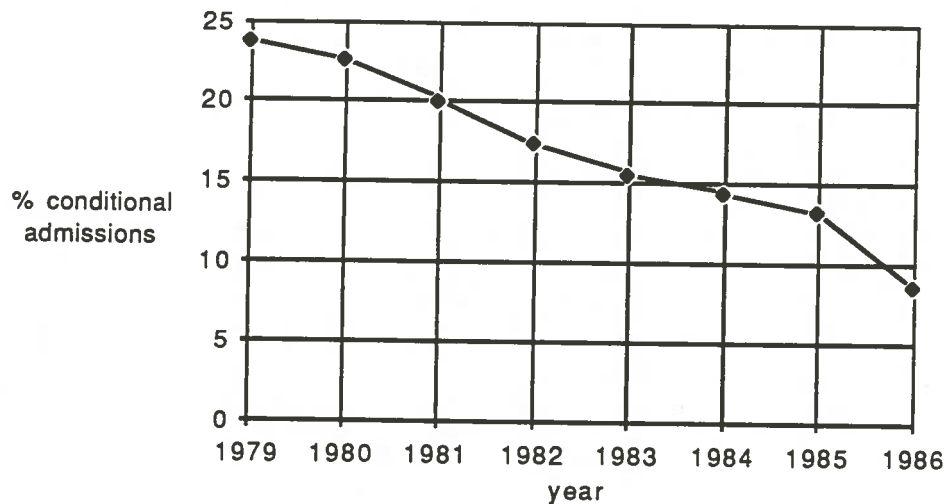
Fig. 2.4. The percentage of students entering kindergarten in Calif. by year from 1979 to 1986 whose vaccine status was classified as conditional at the time of school entry (compiled from CDHS data).

Public schools and private schools have traditionally differed in the percentages of students that are admitted conditionally (i.e., who have not received all required vaccine doses). While the current law requires schools to exclude from classes those students whose

immunizations are not complete, not all schools use exclusion as a means of compliance to vaccine regulations. Partially immunized or unimmunized conditionally admitted students who do not complete the required immunizations pose a health risk to themselves and others. For this reason, the CDHS includes a question regarding the presence of an official exclusion policy in its selective review survey of schools.

Since public schools and private schools have very different infrastructures and financial incentives, it is important to separate these two groups for this kind of assessment. Fig. 2.5 demonstrates that private schools are less likely to have an official exclusion policy and are less likely to have used exclusion as a means of compliance than are public schools (46).

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46. 1983 represents an anomalous year in several categories of data. No significant policy changes were made in that year, nor was funding significantly changed. The well-known drawbacks of survey methods would therefore suggest that these anomalies are likely the result of errors and bias in the collection or recording of data.

Fig. 2.5. The percentage of public and private schools in Calif. with official exclusion policies based on vaccine status by year from 1981 to 1986 (compiled from CDHS data).

Similarly, different types of day care centers have differing rates of exclusion policies. Public and head start centers are more likely to have official exclusion policies and to have excluded children whose immunizations were not up-to-date than are private day care centers (Fig. 2.6).
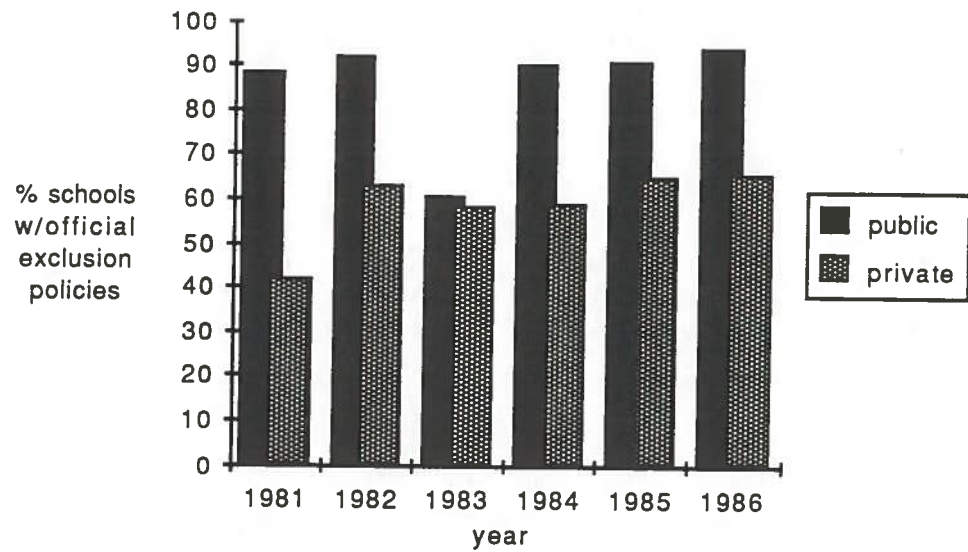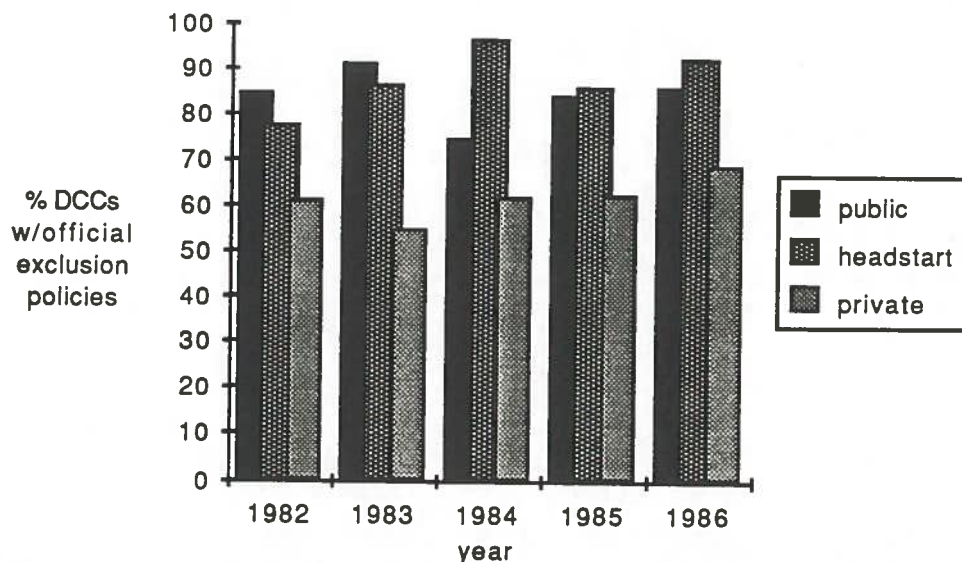

Fig. 2.6. The percentage of public and private day care centers in Calif. with official exclusion policies based on vaccine status by year from 1982 to 1986 (compiled from CDHS data).

Since not all schools and day care centers are strictly enforcing the new regulations, and the law allowed a ten-day grace period prior to 1986, many students who are inadequately immunized start or have . started classes and never receive their missing immunizations. The selective reviews allow the state to examine the extent to which the conditions surrounding the conditional admission grace period were fulfilled. By determining the percentage of inadequately immunized students that actually obtains the missing vaccinations, the state attempts to measure compliance to the school entry laws.

Between the kindergarten reviews, compiled at the time school starts, and the selective reviews, conducted six months later, the schools have time to enforce the regulations and ensure that all conditionally admitted students received the immunizations that they were missing. Private schools and public schools have different rates of compliance to the requirements. Public schools more rigorously follow-up conditionally admitted students (Fig. 2.7).

In Fig. 2.7, a positive percentage change indicates that, at the time of selective review, a greater percentage of children had vaccine status classified as conditional than at the kindergarten survey. This is an undesirable situation. Likewise, a negative percentage change, which is desirable, indicates that some of the children conditionally admitted at the kindergarten survey have received their additional immunizations, and the vaccine status of a lower percentage of the total enrollees is classified as conditional at the time when the selective reviews are conducted.
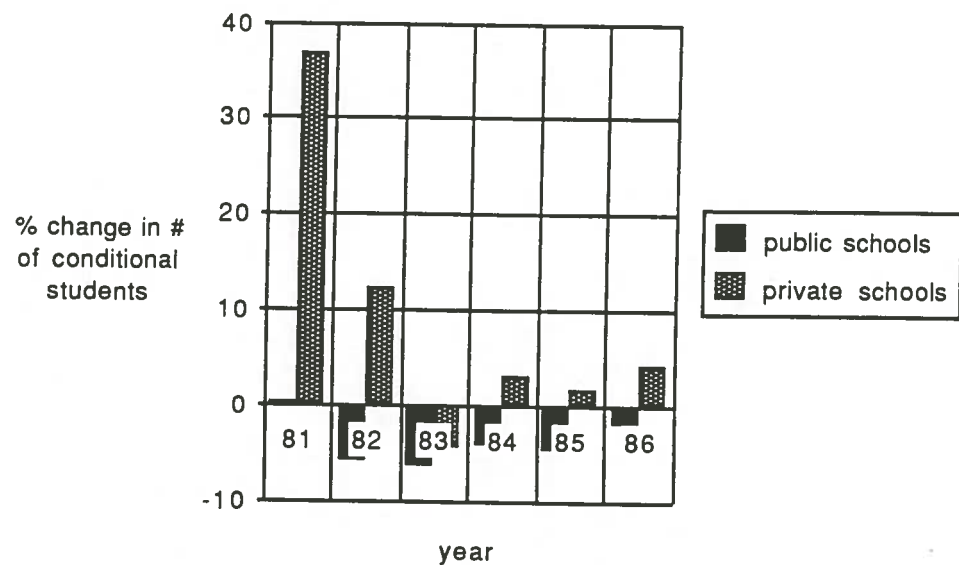
Fig. 2.7. The percentage change in the number of students with conditional vaccine status between school entry and selective review in public and private schools in Calif. by year from 1981 to 1986 (compiled from CDHS data).

Underimmunized Segments of the Population

By retrospectively examining individual immunization records during the selective reviews, the state can determine immunization levels for groups of children at different ages prior to school entry. Such a process reveals that 2 year-old children and 7 month-old children are a particularly underimmunized segment of the population. While the percentage of these children who are adequately immunized has been increasing with time (Fig. 2.8) (47), the immunization levels for these two groups are both considerably statistically significantly lower (p < .00002) than the levels for one year-olds and kindergarteners.

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47. The data presented in Fig. 2.8 was obtained from the CDHS selective reviews and KG surveys.
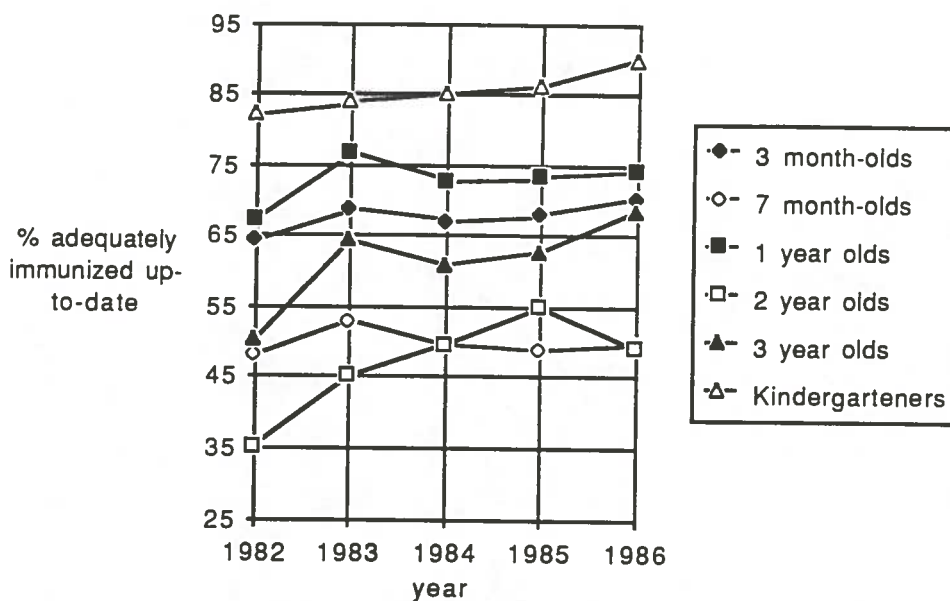
Fig. 2.8. The percentage of California children up-to-date for all vaccine antigens by age group by year from 1982 to 1986 (compiled from CDHS data).

This phenomenon of age-selected underimmunization has been referred to as the "Toddler Gap," and is not unique to California. The state of New York performs retrospective surveys on randomly selected children in the schools that are being selectively reviewed similar to those done by the CDHS (48). Fig. 2.9 depicts the Toddler Gap in the state of New York for the year 1984.

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48.   data from the N.Y. State Department of Health
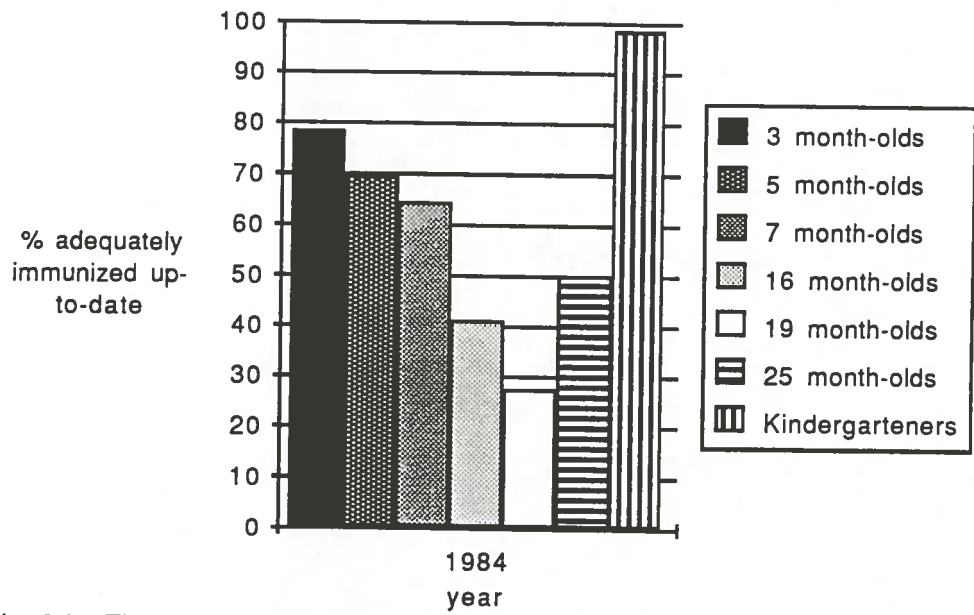
Fig. 2.9. The percentage of children in New York State by age group up-to-date for all vaccine antigens in 1984 (compiled from NYDH data).

Data were also available from similar studies in the state of Massachusetts (49). The data for two year olds up-to-date for all antigens from retrospective studies conducted in 1986 (birth cohort 1980) in California and Massachusetts are compared in Table 2.1. All the evidence indicates that certain age groups of toddlers in this country are grossly underimmunized.

	Measles	Mumps	Rubella	DTP (4+ Doses)	Polio (3+ Doses)
Calif.	55.9%	51.1%	54.8%	49.1%	75.4%
Mass.	60%	58%	56%	66%	76%

Table 2.1. Percentages of two year-olds up-to-date for all antigens in Calif. and Mass., 1986 (compiled from CDHS and MSDH data).

49.   data from the Mass. State Department of Health

While a trend does exist, statistical analysis for California reveals that, with the exception of 1981, there does not seem to be any significant (5% level) variation between the percentages of children whose immunizations are up-to-date at the age of two depending on whether the children attend kindergarten at public or private schools (Fig. 2.10) (50).
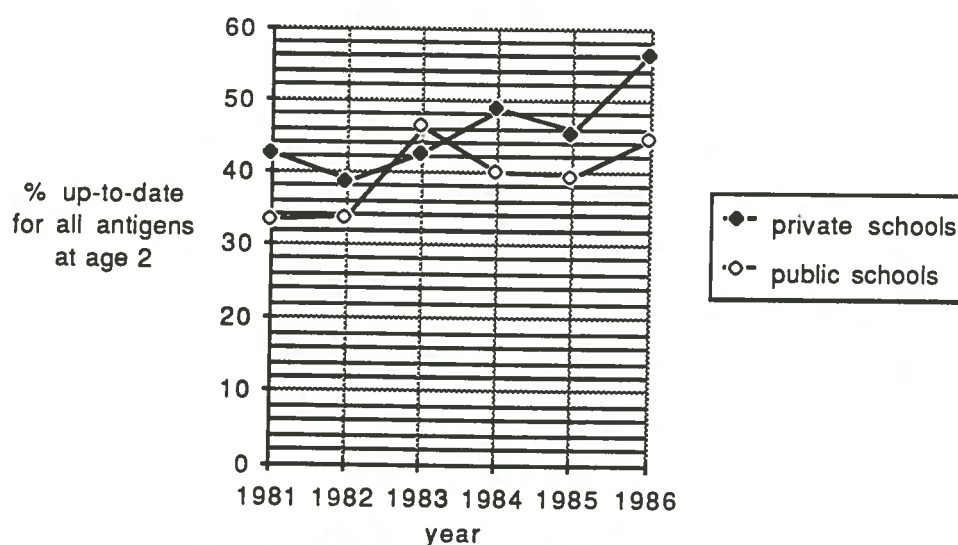
Fig. 2.10. The percentage of 2-year old children up-to-date for all vaccine antigens who later attended either public or private kindergartens in Calif. by year from 1981 to 1986 (compiled from CDHS data).

The consequences of the Toddler Gap are illustrated by a sampling of disease statistics. In 1979 in California, there were 122 reported cases of pertussis. Ninety-two of these cases, 75%, occurred in children under four years of age. Infants under one year of age represented 54% of cases (51). In 1980, California had 147 reported pertussis cases, 78% of which occured in children under

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50.   CDHS data

51.   Centers for Disease Control. Annual summary 1980: reported morbidity and mortality in the United States. MMWR 1981; 28: 61.

four, 54% in infants under one (52). California had 9,477 reported measles cases in 1977, 18% of which occurred in children under four years of age (53). For the nation as a whole in 1983, 52% of persons with pertussis were less than one year old. Of those infants, 73% were hospitalized, 22% had severe pneumonia, 2.6% had at least one seizure, and .7% died. The incidence rate for children under one year of age was about 36.5 per 100,000 population (54).

Discussion

The data presented here demonstrate that immunization levels in California children are increasing, although California still falls slightly below the national weighted average that the CDC reports for percentages of school children who have completed all state-required vaccinations. Recent legislative changes in California have clarified vaccine requirements as well as public health implementation at the school level. Public schools are complying with the new regulations to a greater extent than are private schools and have a lower percentage of students with conditional vaccine status, both at the time of the kindergarten survey and the selective reviews. Young children, especially 7 month-old and 2 year-old children, have disturbingly low immunization levels. This problem is not unique to

52. Centers for Disease Control. Annual summary 1981: reported morbidity and mortality in the United States. MMWR 1982; 29: 62.

53. Centers for Disease Control. Annual summary 1978: reported morbidity and mortality in the United States. MMWR 1979; 26: 58.

54. Centers for Disease Control. Annual summary 1983: reported morbidity and mortality in the United States. MMWR 1984; 32: 40.

the state of California and is not significantly related to a child's later attendance at either a public or private kindergarten.

Immunization levels in children are influenced by several factors, most of which do not operate independently. Public policy and its implementation and enforcement affect immunization levels and are the main concentration of the following discussion. However, access to health care, attitudes about health care, and parental education are also significant and closely related variables.

As immunization levels increase in California, they are approaching the national average. It must be noted that the figures from the CDC depicted in Fig. 2.3 may be under-representative, since not all the states and territories accurately report local data. In addition, the vaccine requirements in California are more rigorous than in many other states. For instance, during the 1985-86 school year, vaccination against mumps, required for all grades K-12 in California, was not required at all for any grade in 17 states and was required only of new entrants or only for grades K-6 or lower in 17 states.

It must also be noted that California is responsible for immunizing a huge population of children, many of whom are immigrants. California is the most populous of the fifty states, with an estimated 1985 mid-year population of 25,575,775. Approximately 433,334 infants are born each year in California, a figure which represents about one-eighth of the children born in the United States, and more than the combination of births occurring

annually in nineteen states and the District of Columbia (55). Furthermore, about 15% of California school children are immigrants. Such a large scale immunization program is most difficult and costly to run efficiently.

In addition, in accordance with the new regulations, children in California are no longer counted as having met all vaccine requirements unless they have a written record showing at least month and year of receipt of every vaccine dose. This is not true in most other states, and may contribute to California's position below the national average. While an increase in the percentage of children who are up-to-date for all antigens in California and, indeed, the nation is obviously desirable, the difference between California and the national average may be misleading.

The new school entry regulations seem to be having some impact on the immunization levels of school children. 1986 represented the biggest yearly decrease during the eight-year period 1979-86 in the percentage of children starting school who were not up-to-date for all antigens. It is anticipated that the fall in conditional admissions will be even more dramatic for the school year beginning in September of 1987, since a considerable number of children had already registered for the 1986-87 school year by the time the new regulations went into effect in March of 1986.

While the 1986 amendments, as indicated above, did manage to decrease the number of students conditionally admitted, the new

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55.   data from Department of Finance.   Population Research Unit, Sacramento, California, July 1, 1985.

regulations did not have a large impact on the follow-up of those students who were illegally or mistakenly admitted. The Immunization Unit of the CDHS finds that under-reporting of conditional admissions through misunderstandings of requirements, particularly those regarding boosters, appears to be the reason why public schools failed to show a greater improvement and private schools showed an actual increase in the number of students classified as conditional at the time of the selective reviews.

The increase in the number of students in public schools whose immunization status was classified as conditional at selective review can occur by either of two means: 1) through the discovery at selective review that children whom the school had admitted as up-to-date were really misclassified and were missing one or more immunizations, or 2) through the admission of more conditional students. Misclassification of immunization status at the initial school survey may be a likely cause for this phenomenon. Selective reviews show that many school personnel misunderstood the immunization requirements for unconditional admission. Commonly, students who had received MMR before their first birthday or all of their DTP/Td immunizations before their second birthday were mistakenly classified as unconditional.

The decrease in the number of students still missing immunizations at the time of selective reviews in the public schools indicates that some students are receiving the vaccine doses that they were missing. At the very least, these data indicate that more children became up-to-date for all antigens than were discovered to have been misclassified. It may also indicate a decrease in the

enrollment of children missing vaccinations who, once excluded from public school, may have enrolled in private institutions.

The selective reviews allow specific problem areas to be identified and targeted for policy changes. Misclassification has just been shown to be one such problem area. In response, the CDHS has gradually condensed the description of requirements that the school admissions officers must deal with from a lengthy handbook in 1977, to a reduced version of the handbook in 1981, and finally to an easy-to-follow one-page guideline in September of 1986.

Financial incentives may help to explain some of the differences noted in the data between public and private schools. The fact that private schools are less likely to have exclusion policies and are less likely to have used exclusion as a means of compliance than are public schools may reflect the fact that private schools more completely depend on full enrollment for continued existence.

In addition to differing financial incentives, perhaps another explanation for the difference in compliance to the admission requirements between public and private schools is the method by which conditionally admitted students are monitored. Both public and private schools are most likely to have a secretary or a clerk doing the follow-up work. But private schools are much more likely to have a principal or director follow-up on the children, while public schools more often have a health aide or school nurse. It should be noted that Proposition 13, passed in 1978 in an effort to reduce property taxes, has resulted in severe cutbacks in personnel in most California counties. Especially hard hit have been the school nurses. While the nurses have more or less regained their strength in

numbers, the duties required by each school nurse have increased dramatically, allowing much less time for the administrative efforts involved with vaccine-related exclusion (56).

The Toddler Gap has been demonstrated to be a major health problem, both in California and the nation as a whole. Perhaps one reason that toddlers are so underimmunized is the lack of a convenient point in time, such as the commencement of school, at which a law can be enforced requiring toddlers to be immunized. While this has been done in California and other states for children attending child care centers, obviously not all children attend such institutions.

The Toddler Gap was another problem area that was identified through the use of selective review. In 1986 the CDHS implemented programs to try to ensure that 90% or more of the children born in California each year are up-to-date for all antigens by age two. These programs included increased emphasis on hospital-based education programs for new mothers, involving WIC and other organizations to include immunization as a criterion for receiving other infant and toddler care, and improving education by health care providers with such items as "Date Next Immunization Due" stickers for the outside jackets of the child's immunization record.

A child's attendance at a public or private school might serve as a proxy for the family's socioeconomic status (SES). Therefore, upon initial examination, the results from Fig. 2.10 may seem surprising. It would seem logical that children from higher income

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56.   personal communication with Calif. School Nurses Organiz.

families attending private schools have fewer barriers to health care access and parents with higher levels of educational attainment than many of the children attending public schools. Given that, children at private schools should therefore have higher levels of immunization. However, the fact that there is no statistical difference between the two groups may reflect characteristics of both health care utilization and school populations.

Public school populations examined in aggregate at the state level rather than by school district, usually do not represent just the children of lower income families. They are usually comprised of a cross-section of the state's entire population. A true difference in vaccination levels between high income and low income families may be masked by using public vs. private school as a proxy for SES. Furthermore, it is not necessarily the very poor who have the greatest barriers to health care access because they are provided for to some extent by MediCal. It is the section of the population who do not qualify for MediCal but also cannot readily afford good health care who may be at the greatest risk for under-immunization. This section of the population may be growing as eligibility requirements for MediCal become more stringent.

It is interesting to note that more highly educated parents may also be more aware of the possibility of adverse reactions to vaccinations than other parents and therefore actually more hesitant to submit their children to immunization. More careful studies examining the link between health care access and immunization levels need to be performed. Regardless of the family's SES, it can still be stated that toddlers as a general group are grossly

underimmunized.

Weaknesses in the Monitoring System

Selective reviews also point out some of the weaknesses of the current immunization level reporting and surveillance systems. School records are used for this system, and the selective reviews consistently point to a recurring problem of misclassification of students' vaccine status. The new regulations requiring written immunization records from physicians or clinics as documentation of immunization should help alleviate this problem. A recent case-control study of a measles outbreak in California showed a higher odds ratio (i.e., risk) for those children with school records indicating that they were immunized but for whom a doctor-verifiable record was not obtained than for those children who had doctor-verifiable school records (57).

Summary

In conclusion, immunization levels in California children are rising. Despite the fact that incidence rates for many infectious diseases are less than five percent of those during the pre-vaccine era, troublesome levels of vaccine-preventable illnesses still occur in California today. Differences exist in immunization levels and policy implementation in public and private schools. These differences stem largely from differing administrative structures and

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57. CDHS data

responsibilities, financial incentives, and populations. Tougher regulations regarding school entry have improved vaccination levels but need to be more strictly enforced, especially in the private schools. Toddlers, especially children in the seven-month and two-year age brackets, represent a very vulnerable and underimmunized portion of the population, both in California and the nation as a whole.

Policy Implications

Efforts must be strengthened and continued in order to raise toddler immunization levels to an acceptable level. Perhaps an efficacious way of effecting increased levels of immunization in the toddlers would be increased health education efforts. The mass media is not used often enough as a tool for imparting knowledge about good health care. A successful advertising campaign should be undertaken to alert parents of the danger that their toddlers are in from the morbidity and mortality of vaccine-preventable infectious diseases. Such an effort was undertaken with considerable success in Great Britain in 1982 at the height of a pertussis epidemic. While many academics have traditionally disregarded the potential of such media campaigns, extensive national campaigns have been shown to produce positive public health behavioral changes in many areas, such as smoking cessation and dental hygiene (58,59).

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58. Flay BR. Mass media and smoking cessation: a critical review. Am J Public Health 1987; 77: 153-60.

59. Schou L. Use of mass media and active involvement in a national dental health campaign in Scotland. Community Dent Oral Epidemiol 1987; 15: 14-8.

In addition, pediatricians and family practitioners need to be made more aware of the existing problem of underimmunization so that they will be encouraged to take a more active role in ensuring toddler vaccination. Reminder cards, similar to those frequently used by dentists for six-month check-ups, might serve as an effective means of increasing immunization levels in this vulnerable and largely helpless age group.

The selective reviews provide valuable information regarding current immunization levels of California's children, and they serve as a useful tool for the evaluation of public policy implementation. Other states should be encouraged to adopt this method, thereby allowing for a more accurate evaluation of national immunization levels.

Misclassification represents a large source of error in California's current immunization data. Recent changes in laws concerning school documentation should help to alleviate some of the error resulting from misclassification.

Chapter Three

VACCINE-RELATED INJURIES IN CALIFORNIA

Introduction

In the eighteenth century, when the medical care that could be provided for patients suffering from infectious diseases was at a bare minimum by today's standards, people were fairly willing to accept condiserable risk in order to gain protection from dreaded diseases. George Washington felt that one in 300 deaths from variolation was an acceptable risk to protect his fighting force from the scourges of smallpox. The Bills of Mortality from the late eighteenth century in London indicate that about two out of 17 deaths were due to smallpox, while the case mortality from inoculation varied between one in 60 in Boston and one in 91 in England. The final reports compiled by the Royal Medical Society for 1721-28 for the British Isles, American Colonies, and Hanover show that of 897 inoculations, 17 resulted in death, about one in 50. In 1922-23 in England and Wales there were 62 cases of post-smallpox vaccination encephalitis (60).

Despite the immense progress that has taken place in the research, development, and distribution of safe and effective vaccines since that time, a fundamental problem still exists with any vaccination program. Adverse reactions pose an unavoidable risk that accompanies any individual dose of vaccine that is administered. The majority of adverse reactions are mild and self-limiting and are typically seen as pain and itching or redness at the site of injection (61). Therefore, for the majority of individual vaccinees, and

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60. Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 234-5, 352-4.

61. Office of Technology Assessment. A review of selected federal vaccine and immunization policies. Washington, D.C.: Congress of the United

consequently for the community as a whole, the benefits derived from effective vaccination programs greatly outweigh the costs. Yet for a very small percentage of the population, the costs of vaccination may manifest themselves as permanent disability or even death and clearly outweigh the benefits.

Objectives

This chapter is devoted to a discussion of adverse reactions following vaccination. A brief historical context has already been provided. Various adverse reactions and the mechanisms by which they are thought to cause harm are discussed, and the response of the general public to adverse reactions is illustrated using examples from Britain and Japan. The monitoring system for adverse reactions following immunization for both the state of California and the federal government are described, and some of the weaknesses of each are pointed out.

With this information as background, the current trends in the rate, number, and severity of adverse reactions in California, as well as differences in these variables between the public and private health care sectors is presented. The following chapter examines adverse reactions to pertussis (whooping cough) vaccination in much greater detail.

Adverse Reactions Following Immunizations

There is a broad continuum of adverse reactions to most

States, 1979: 83.

vaccines. Local reactions, rashes, and fevers are common following DTP (diphtheria, tetanus, and pertussis) vaccines and MMR (measles, mumps, and rubella) vaccines. Allergic reactions may range from hives to life-threatening systemic anaphylaxis. Arthritis and arthralgia are fairly common occurrences following the administration of several vaccines, but are nearly always time-limited. Several nonspecific complications that commonly follow immunizations include persistent screaming or crying, fussiness, or loss of appetite.

The most serious complications from vaccinations affect the central nervous system. Febrile convulsions are probably the most common neurological adverse reaction, but are not a direct effect of vaccination. However, non-febrile seizures, convulsions, encephalitis, and encephalopathy occur infrequently and may leave permanent neurological residua. Perhaps the most prominent recent example of neurological damage was the alarming number of cases of the Guillan-Barré syndrome following "swine" influenza immunizations in 1976. Poliomyelitis may occur after the administration of oral polio vaccine (OPV), and Reye's syndrome, an often fatal disease of children involving the nervous system, the liver, and the kidneys, has also been reported following immunization in very rare instances.

The biological mechanisms through which each vaccine may cause an adverse outcome varies with the antigen and the vaccine preparation that is used. The fevers and febrile convulsions caused by whole cell vaccines are often attributed to the presence of endotoxin in the vaccine dose. Endotoxin is a bacterial component

that causes cells of the human immune system to release endogenous pyrogen, a substance which can "reset" the hypothalamic temperature regulation, causing a loss of control of core body temperature.

Other adverse reactions are mediated by different immunologic mechanisms and can be classically allergic in nature, caused by prior sensitization to substances such as chick embryo materials that are frequently used in vaccine production. Adjuvants, foreign materials that are added to vaccines to increase their immunogenicity, can also cause direct or indirect adverse reactions.

Implications of Adverse Reactions

Unlike eighteenth century populations, modern societies are far less willing to accept complacently the risks associated with immunization. Perhaps no modern episode demonstrated the fragility of the public acceptance of vaccination programs more than the events that transpired in England in the early 1970's. In Britain, trials for a pertussis vaccine began in the late 1940s. By 1957 pertussis immunization was included in the nationally advised immunization policy. In January of 1974, a report linking neurological complications to pertussis immunization in 36 children at a London hospital over a twelve-year period was widely publicized (62). The press and television accounts of these reactions caused such a public stir that demands for an enquiry into British

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62. Kulenkampff M, Schwartzman JS, Wilson J. Neurologic complications of pertussis inoculation. Arch Dis Child 1974; 49: 46-9.

vaccine policy were made in Parliament. Following this publicity, the acceptance rate for pertussis immunization in England fell from 79% in 1973 to only 31% in 1978 (63). Consequently, in 1977-79, England experienced the worst whooping cough epidemic since national immunization practices were enstated in 1957.

During those two years, there were 28 deaths from whooping cough in England and Wales in unimmunized children, 5,000 admissions to the hospital, 200 cases of pneumonia, and 83 cases of convulsions related to whooping cough. During the three-year National Childhood Encephalopathy Study in Britain, there were only two deaths following neurologic complications that had onset within seven days of pertussis immunization (64).

Studies conducted during the peak of the British outbreak illustrate the protective effect of the pertussis vaccine. Seven out of ten unimmunized siblings of primary cases contracted whooping cough, while only two out of ten vaccinated siblings contracted the disease.

A similar phenomenon occurred in Japan. After two deaths occurred in children who had been vaccinated with DTP in December, 1974 and January, 1975, the Administration of Health and Welfare discontinued DTP immunization programs for a brief period, until April, 1975. However, public acceptance was slow to return, and the immunization rate was very low for several years. Consequently,

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63. Robinson RJ. The whooping cough immunisation controversy. Arch Dis Child 1981; 56: 577-80.

64. Valman H. Whooping Cough. Br Med J 1982; 284: 886-7.

there were 31,730 notifications of pertussis in Japan during 1975-79, up from 1,887 in a similar four-year interval from 1970-74. The incidence rate of pertussis rose from 0.4/100,000 people in 1974 to 8.4/100,000 in 1978. There were no pertussis deaths in Japan in 1974, while during the period 1975-1979 there were 118 pertussis fatalities in infants and children (65).

Assessing the Problem: Surveillance Systems

Careful monitoring of vaccine outcomes and adverse events following immunization can help to identify some potential dangers associated with vaccines, identify specific manufacturers' lots of vaccine which may be particularly dangerous (such as the Cutter polio lots) (66), and help to avoid the disastrous public health consequences of unnecessary panics such as those that occurred in England and Japan.

In California, adverse reactions to vaccines administered through the public sector are monitored through the California State Department of Health Services (CDHS) in conjunction with the national Centers for Disease Control (CDC) via a cooperative program entitled the Monitoring System for Adverse Events Following Immunization (MSAEFI). Adverse reactions to vaccines administered within the private sector are also monitored by the CDHS in

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65. Kanai K. Japan's experience in pertussis epidemiology and vaccination in the past thirty years. Jpn J Med Sci Biol 1980; 33: 107-43.

66. In 1955, doses from seven improperly inactivated vaccine lots manufactured by Cutter Laboratories in Berkeley, California caused active cases of paralytic poliomyelitis and even death.

conjunction with the Food and Drug Administration (FDA).

The MSAEFI system begins at the clinic or health care provider's office. It is initiated when, in public clinics supported by county health departments, an adult patient or the parent or guardian of a minor patient is given an informed consent form. This form describes the risks and benefits of the particular vaccines that are to be administered. Unfortunately, during the time period that the data presented here were generated, the obtainment of written informed consent was not legally required in private health care settings. Therefore, it was often not obtained by private health care professionals prior to vaccine administration. If informed consent is obtained in the public clinic, the patient or parent keeps part of the form describing what types of adverse reactions are frequently encountered following vaccination. This paper also includes the telephone number of the county health department and instructions to call in the event of an illness within four weeks following the immunization. The vaccine dose is then administered.

If an illness occurs, the parent or patient associates this illness with the vaccine, and the parent or patient remembers the form, then he or she will telephone the county health department. Frequently, a family physician, who may or may not have administered the vaccine, is called directly. It is the physician's obligation to notify the county health department of such adverse reactions, though if the patient or family does not inform him or her that an immunization occurred recently, he or she won't know about the possibility of an adverse reaction.

Reports of adverse reactions are forwarded by county health

departments to the Immunization Unit of the CDHS in Berkeley. A CDHS physician reviews all reports, and if the reaction required hospitalization or a visit to a health care provider, then the reports are forwarded to the CDC in Atlanta. Federal policy dictates that even if medical care was obtained, reports of local reactions involving only soreness, redness, or swelling in the immediate vicinity of the injection site are not reportable to the CDC. It is therefore worth noting that some level of screening takes place at the state level. The information is reviewed at the CDC, and missing information is actively sought after via telephone by the California Immunization Unit.

Such a reporting system can be described as stimulated passive reporting. It is stimulated in the sense that descriptions of the more common reactions as well as specific telephone numbers are provided to the patients. Additionally, missing information is actively acquired, usually by telephone. However, this system is passive in the sense that someone must contact either the county or the physician in order to initiate the reporting process. The county does not routinely question the outcome of each vaccination event.

If the county were to question the outcome of each event, then the system would be one of active surveillance. Active surveillance is generally recognized by epidemiologists as a far more accurate process than passive or even stimulated passive reporting. However, with the number of vaccine doses administered each year in California totaling in the millions, a system of active surveillance, while ideal, would be impossible and represent an inefficient allocation of scarce resources.

Monitoring of reactions following immunizations with vaccines administered in the private sector is a similar process. However, private sector reports use a more narrative format and are forwarded by the CDHS to the FDA rather than the CDC. Thus, all reports of adverse reactions following immunizations in California should be reviewed by a CDHS physician. Therefore, the CDHS plays an important initial screening role for all reported adverse reactions.

Problems with the Monitoring System

Probably the biggest drawback to these stimulated passive reporting systems is under-reporting. For instance, from 1982-84, 23 cases meeting the case definition of poliomyelitis were reported from across the country through the polio surveillance system to the Division of Immunization of the CDC. Thirteen of these cases were in recipients of OPV vaccines, and ten cases were in contacts of OPV recipients. Only one of the 13 cases was also reported to MSAEFI, and it came from the private sector (whose reports are supposed to go to the FDA) (67). The CDC reports that some 20.895 million public doses of OPV were administered during 1982-84, representing 34.3% of the total doses distributed in the United States. That means that there was a total of 60,918,367 doses of OPV administered. This fact would suggest that paralytic polio occurred in OPV recipients at a rate of at least 13/60,918,367 or about .21 per million doses.

If polio in contacts of vaccine recipients is included, the serious

67. all national data from: Centers for Disease Control. Adverse events following immunization. Surveillance Report No. 2, 1982-1984. Issued December, 1986.

adverse reaction rate for OPV becomes at least 23/60,918,367 or about .38 per million doses. This result is very similar for the figures reported for the twelve-year period 1969-80, during which time approximately 290 million doses of OPV were distributed with 92 cases of associated paralysis, giving a rate of .32 per million doses (68). During the period 1982-1986 there were three reports of paralytic illness following OPV administration in California. All three showed some level of partial recovery after 30 days. These numbers illustrate the vast magnitude of the under-reporting problem.

The CDC also identifies nine other shortcomings of MSAEFI (69).

1) In addition to under-reporting, non-standardized data collection is a problem. Information is often obtained from mothers or other family members rather than physicians, and the recording of this information is often performed by nonmedical personnel. 2) There is difficulty in separating data transcription errors from vaccine administration errors (eg. a report following DT immunization in a child over age seven who should have received Td).

3) All public sector reports received by the CDC are included in the MSAEFI data base, so inclusion of events which may not be related to immunization occurs. 4) Since all the reports are initially screened by the state health departments, variability may be introduced by different interpretations of the reporting requirements. 5) Missing data cannot always be obtained by telephone, so some reports are incomplete. 6) The simultaneous administration of several vaccine antigens is a common and cost-effective practice. However, it is impossible to

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68. Centers for Disease Control. Recommendation of the Immunization Practices Advisory Committee. MMWR 1982; 31, 3: 22-6, 31-4.

69. The description of the weaknesses of the monitoring system is largely derived from that provided by the CDC in: Centers for Disease Control. Adverse events following immunization. Surveillance Report No. 2, 1982-1984. Issued December, 1986.

isolate which antigen may have been responsible for any given reaction if multiple antigens were administered. Frequently a 15-month-old child will receive nine different antigens at one time (DTP, trivalent OPV, and MMR).

7) Lack of long-term follow up is a problem. The patient is called by the state seven days after the onset of symptoms. If the patient is not recovered at that time, a second call is placed 30 days after the onset of symptoms. 8) Temporal reporting bias can also influence reporting, since people are more likely to link an illness to a possible causative factor (such as immunization) if the illness follows soon after this factor. There is probably a bias towards reporting events occurring soon after vaccination as opposed to those occuring one to four weeks later. This may lead to the under-reporting of delayed but serious adverse events. It should be noted, however, that a short time span between vaccine administration and illness onset is usually considered to strengthen the possibility of a causal relationship.

9) Finally, the CDC recognizes a lack of background data as a significant problem. Without such data, it is difficult to establish whether an event temporally related to immunization is occurring more frequently than the expected rate of such an event due to other causes. It must be emphasized that temporal associations do not necessarily indicate causality.

Unfortunately, several other considerations need to be added to this lengthy list of problems. There is often a lack of a particularly distinctive syndrome associated with adverse reactions to any given vaccine. Therefore it is difficult for a physician to recognize that an illness may be associated with a vaccine or to ascribe a causal role to the vaccine. Even when certain signs and symptoms typically signify an adverse reaction, measures such as fretfulness or persistent crying are very difficult to quantitate.

In addition, vaccines are administered by a wide range of health care professionals. Some adverse reactions may be the result

of errors in vaccine administration rather than toxicity inherent to the antigen. One of the difficulties that also must be faced when dealing with adverse reactions, especially the serious ones, is that the numbers of reactions are very very small. Statistically significant differences are therefore very hard to detect, and effective studies must necessarily include extremely large study populations.

The Magnitude of the Problem: Adverse Reactions in California

As can be seen in Fig. 3.1, since 1982 the total number of adverse reactions reported to the CDHS (from both the public and private sectors) each year has increased, from 154 reports in 1982 to 252 reports in 1986, a 64% increase over the five-year period. This mirrors the overall national trend, as the CDC received 1,698 reports in 1984, up from 990 in 1979, a 71% increase.
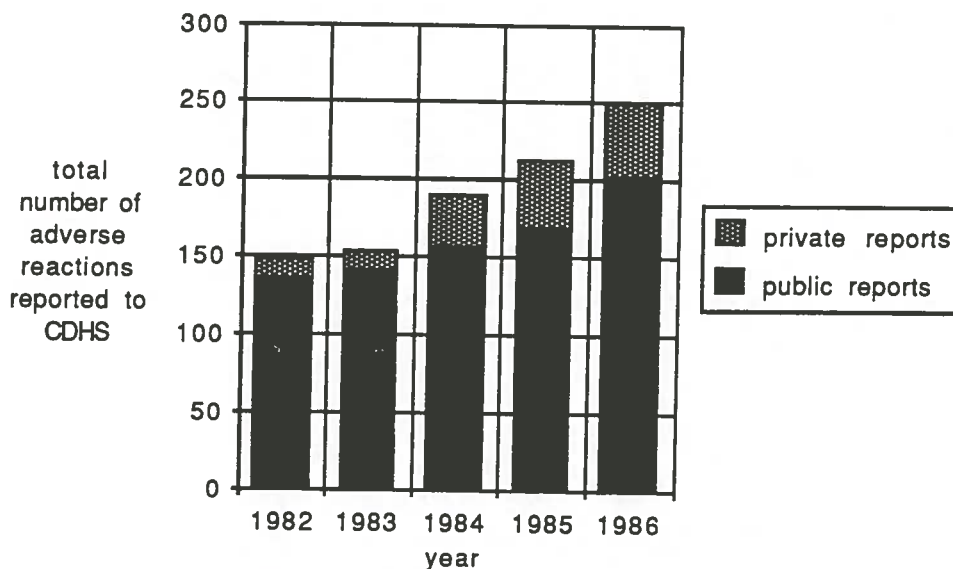
Fig. 3.1. The total number of reports of adverse reactions following immunizations in Calif. received each year by the CDHS from 1982 to 1986 (compiled from CDHS data).

Such a large increase in the reported number of adverse

reactions poses a very interesting question: what is responsible for the increase? Is this a real increase or a reflection of a secondary phenomenon? It may indicate an actual increase in the number of adverse reactions occurring. Alternatively, it may simply reflect an increase in reporting. Such an increase in reporting may be attributable to increased awareness about the reactions or improved reporting formats.

Since the number of public vaccine doses administered each year in California did not increase as fast as the reports of adverse reactions, the *rate* of adverse reactions resulting from immunizations with public vaccine in California during the period 1982-86 also increased, from 72.8 per million doses in 1982 to 92.08 per million doses in 1986, an increase of 26% (see Fig. 3.2).
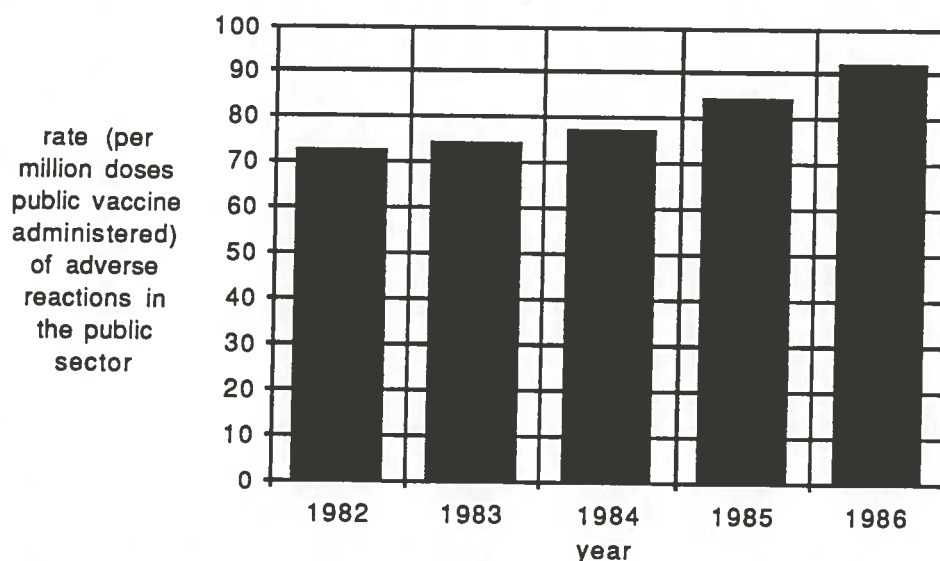

Fig. 3.2. The reported rate of adverse reactions following immunizations provided by the public sector in Calif. by year from 1982 to 1986 (compiled from CDHS data).

These annual figures result from counting all reports of adverse reactions received by the CDHS from the public sector for each year and dividing by the total number of public vaccine doses

administered in that year. When calculating the number of public doses administered, each MR is counted as two doses, and each MMR is counted as three doses in accordance with CDC guidelines. This is done because MMR vaccine, although it is usually administered as only one injection, includes three antigens.

Because the CDC uses different criteria for reporting adverse reactions, the rates are lower (combined rate for 1982-84 of 67.9/million public doses) if the CDC requirements are used to also determine the numerator. As mentioned above, the CDHS will only forward a report to the CDC if the recipient was hospitalized or seen by a health care provider. However, the CDHS has a lower reporting threshold and will accept any report of an adverse reaction, even if the health care provider or county was contacted only by telephone. Therefore, while by CDC criteria the national rate is lower than the CDHS rate, it probably represents a higher proportion of more serious reactions, since each person was sick enough to warrant medical attention. Once again, since these data reflect the increase in the number of reports of adverse reactions, it is unclear whether or not they represent an actual increase in the rate of adverse reactions.

Total population rates of adverse reactions cannot be calculated for California for several reasons. 1) The rates of adverse reactions in the private sector cannot be determined. While individual vaccine lots used in the public sector are monitored by the state, the manufacturers of the vaccines are not required to divulge to the state the total number of doses that they have distributed in the private sector. Therefore, no denominator is available with which to calculate a rate of adverse reactions following privately administered

vaccinations. 2) Under-reporting within the stimulated passive surveillance system precludes the determination of an accurate denominator even within the public sector. 3) Without a comparison group or accurate background rates, it is difficult to infer causality within certain disease groups, and therefore difficult to develop a true reaction rate.

Serious Adverse Reactions

The CDHS Immunization Unit classifies serious or unusual reactions as anything other than a local reaction, a fever of less than 105'F, or a non-allergic rash. Fig. 3.3 demonstrates that the proportion of adverse reactions reported to the CDHS that are classified by the state as serious or unusual increased over 40% during a five-year period, from around 15% of the total reports in 1982 to almost 56% in 1986.
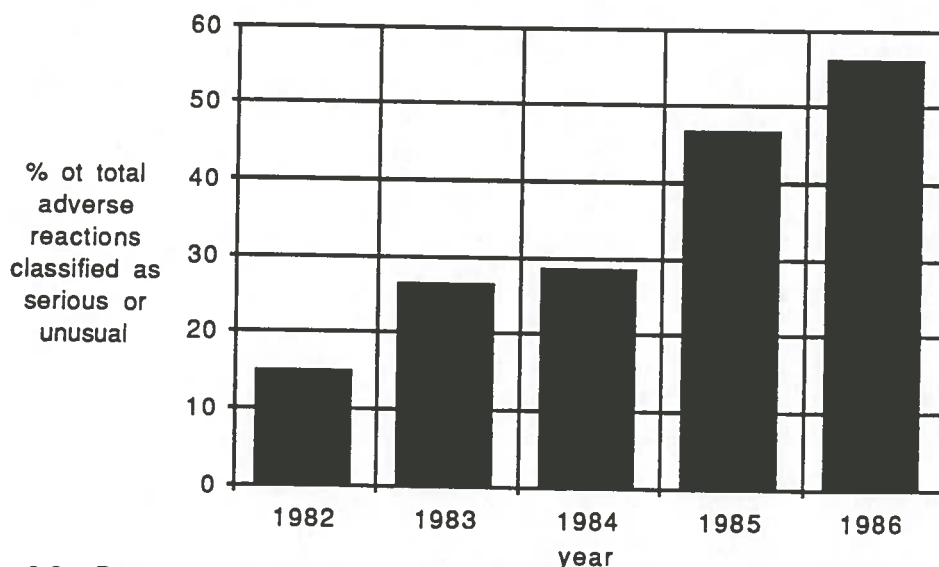
Fig. 3.3. Percentage of total reports of adverse events following immunization in Calif. received by the CDHS classified as serious by year from 1982 to 1986 (compiled from CDHS data).

Such a large increase may reflect the fact that more serious

reactions are occurring, or the fact that reporting for serious reactions is increasing faster than overall reporting in California. As already seen, between 1982 and 1986 total reporting in California increased 64%. During that same period the number of reports of serious events increased from 23 in 1982 to 141 in 1986, an increase of 513%. These figures suggest that the latter situation is the case.

One explanation for this finding may be recent changes in data collection by the CDHS. The CDC reports that for the nation as a whole during the period 1982-84, only 947 reports (25% of the total) were classified as other than fever, local reaction, or rash. Until 1984 in California, serious events were recorded at the CDHS as line-by-line listings by hand. As can be seen in Fig. 3.3, until 1984 the proportion of serious reactions in California was very close to the national average of 25%. However, in 1985, the year of the significant increase in California's reporting, the line-by-line listings for serious reactions were computerized, making data entry and classification much easier. It is interesting to note that, in contrast to California, at the national level from 1979-1984 increases in reporting levels were up much higher for the less serious events (209%) than for the more serious events (53%).

Since the last quarter of 1984, the serious and unusual reaction reports received by the CDHS have been separated into public and private sources. There is a great difference between the proportion of total public sector reports that are classified as serious or unusual and the proportion of total private sector reports similarly classified. Fig. 3.4 illustrates the fact that the private sector has a much higher proportion of very serious reports.
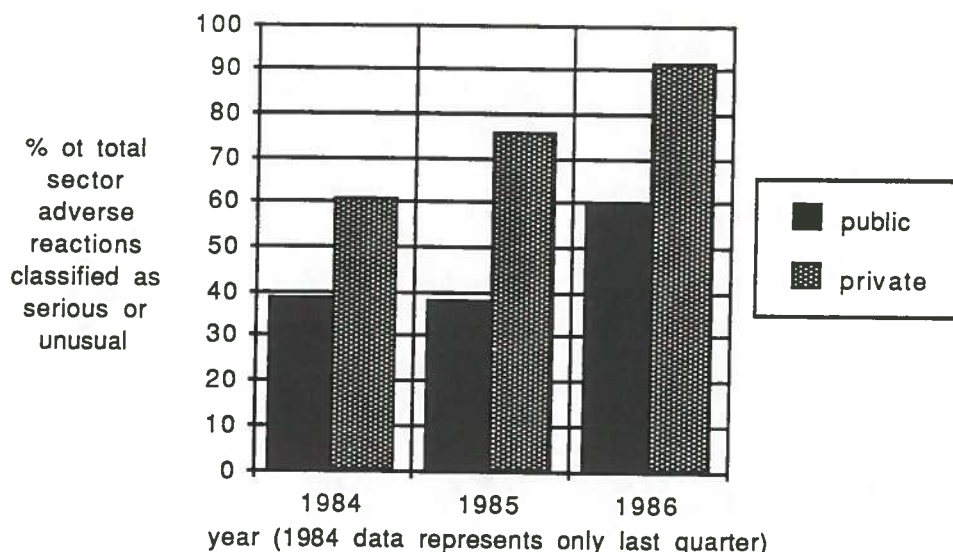
Fig. 3.4. Percentage of total reports of adverse events following immunization in California in the public and private sectors classified as serious or unusual by year from 1984 to 1986 (compiled from CDHS data).

It must be emphasized that this difference between the two sectors does not necessarily mean that the private sector is actually experiencing many more serious adverse reactions than the public sector. This differential may indicate that the private sector is not reporting the less serious reactions with as great a frequency as the public sector. An alternative explanation is that the public sector is not reporting serious adverse reactions as frequently as they should. The true explanation for this observed trend is probably a combination of these two factors.

During the time span 1982-1986 there were 48 deaths that occurred within thirty days of vaccination in California. Twenty-five of these occurred after DTP/OPV (which are often given at the same time) administration, 11 after DTP alone, and 8 after influenza. Twenty-seven of these deaths were SIDS or encephalopathy-related deaths in infants. By definition all of the SIDS deaths occurred in children under age one. Since MMR is not recommended in California

until 15 months, no SIDS deaths are expected following MMR.

Of the 8 influenza vaccine-related deaths 2 were due to the worsening of congestive heart failure, 2 were due to the worsening of diabetes mellitus and hypothyroidism, and 1 was due to aspiration pneumonia. The mean age at death for those dying within thirty days of receipt of an influenza shot was over 72 years. If the youngest patient is not included, the mean age at death for seven of these eight was over 76 years.

The unexplained deaths, however, cannot readily be attributed to adverse reactions to vaccinations. In the absence of good background data, it is difficult to estimate what the probability is that these unfortunate individuals might have died from the same diseases in the absence of vaccination. The relationship between SIDS and pertussis vaccination is explored in detail in a later chapter.

Vaccine Lot Variability and Adverse Reactions

One way of determining if the relationship between serious or fatal adverse reactions and immunizations is causal or not is the examination of a dose-response curve. The existence of a biological gradient makes a causal interpretation much more plausible. Put in the form of a logical question: do more potent vaccines cause more serious reactions? The FDA measures the potency of DTP vaccines by means of an immunological test in mice from which each individual lot of vaccine "scores" a number known as Pertussis Mouse Protection Units. The higher the number is the more potent the vaccine is (i.e. it requires less vaccine to induce a certain level of immunity in the test population). Every DTP vaccine lot manufactured by a company is

tested against this scale.

In California, the manufacturer's lot number is recorded as part of MSAEFI for each adverse event. Appendix Three shows a breakdown of the serious events following immunizations in California from 1982-85 by manufacturer's lot number and gives the weighted averages of their potency. Fig. 3.5 (adapted from CDHS Immunization Unit data) reveals the apparent lack of association between DTP potency (as rated on the Mouse Protection Units scale) and the rate of serious adverse reactions resulting from immunization. A Chi-squared test for trend indicates that there was no dose-response predicted by the strength of the Mouse Protection Units (Chi-squared analysis, test for trend = 0.0610123, p=0.79).
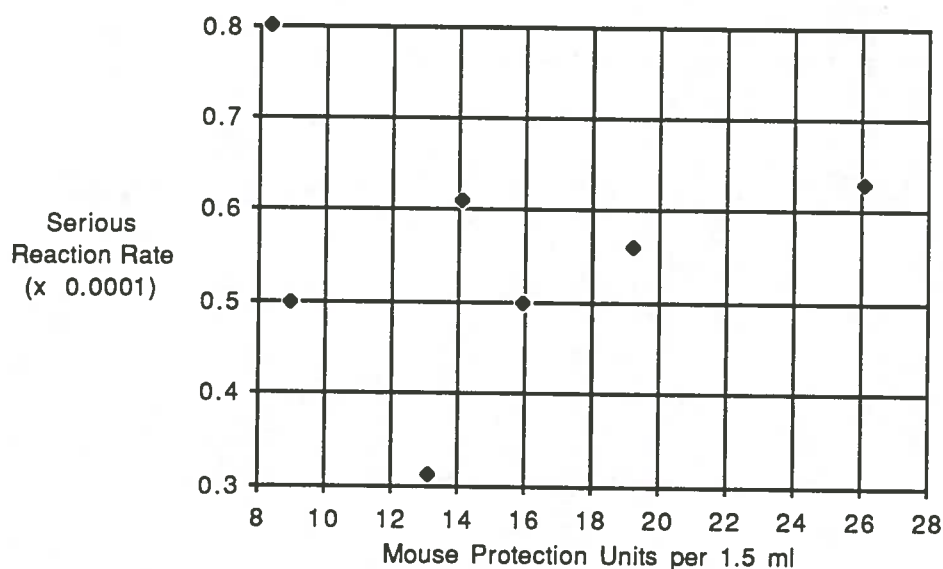
Fig. 3.5. Office of Biologics Pertussis Mouse Protection test results plotted against the rates of serious adverse events in infants/children following immunization with specified DTP vaccine lots in California, 1982 to 1985 (compiled from CDHS data).

In addition to a biological gradient, several other factors are generally considered to support a causal relationship between illness following immunization and the vaccine. Other evidence would be

that the illnesses are 1) clinically distinctive, 2) restricted to immunized children, 3) closely related in time to immunization, 4) associated with a biologically plausible pathogenesis, and 5) without alternative explanation (70).

Policy Implications

The collection of data that has been presented in this chapter suggests the necessity for several policy changes. Short of active post-immunization surveillance, the following suggestions may help to improve the accuracy and representativeness of adverse reaction data. Health care providers must be made more aware of the importance of the accurate reporting of adverse events following immunization. The necessity for this improvement was illustrated by the national polio data which shows the magnitude of under-reporting of even extremely serious diseases that exists in this country today. Reminder notices delineating the reporting procedures and emphasizing the importance of MSAEFI could be distributed by local county health departments to all practitioners, public and private, who are administering vaccinations in a community.

The merits of active surveillance over passive surveillance are well-known by all epidemiologists, and any shift that would make the MSAEFI more active would be beneficial, although costly. But even at a basic level, phone calls could be made on a quarterly basis by county health employees to physicians who are known to

70.	Miller DL, Ross EM, Alderslade R, et al. Pertussis immunisation and serious acute neurological illness in children. Br Med J 1981; 282: 1595-9.

administer a number of vaccines in an effort to stimulate reporting before the more minor reactions are forgotten forever. Alternatively, county health officers could request entrance to meetings of local medical societies to make brief reminder announcements. Little can be done in a cost-effective manner to address the majority of the other shortcomings of the current surveillance systems that were already discussed.

It should be noted that recently enacted federal vaccine injury legislation (PL 99-660) includes several measures aimed at increasing reporting levels of adverse reactions to vaccinations. This law makes reporting of adverse events following immunization mandatory in both the public and private sectors. Physicians failing to report adverse reactions about which they have knowledge will risk prosecution. Written informed consent will also become legally mandatory for all routine immunizations administered in the United States in both the public and the private sectors. These laws are currently targeted to become effective in October of 1988. The extent of enforcement and the impact of PL 99-660 remains to be seen.

Also at the national level, more information must be obtained about the background rates of the diseases that are frequently linked to adverse reactions to immunization as well as the vaccine-preventable diseases themselves. Without these background rates, comprehensive and judicious examination of the safety and efficacy of our current vaccine programs is difficult if not impossible. In addition, tests must be developed that will give some sort of biological standard that may be predictive of severity of reactions to

vaccines. If this can be accomplished, dangerous manufacturer's lots may be recognized before they are distributed, rather than recognized as the result of a clustering of serious or fatal reactions resulting from their administration.

Summary

In summary, it can be seen that changing social and biological conditions over time have made people less willing to accept the possible risks associated with vaccinations. However, these risks, though new technology has minimized them, will always be inherent in the immunization process. The monitoring systems for adverse events following immunization have been described for California and the nation as a whole. This stimulated passive system has several drawbacks which were discussed.

Both the number of reports and the rates of adverse reactions temporally associated with the administration of public sector vaccines in California and the nation are on the rise. In addition, the proportion of total adverse reactions that are classified as serious has risen dramatically in California. The increases in reports of serious reactions are outstripping the overall increases in reporting. In addition, the proportion of reports classified as serious from the private sector is much higher than that from the public sector. The policy implications generated from these data were also discussed.

Chapter Four

PERTUSSIS IMMUNIZATION

Introduction

The previous chapter gave a discussion of the historical context of adverse reactions to vaccinations and delineated the current trends of such reactions in California. Data were presented demonstrating that the majority of adverse events following immunization both in California and the nation as a whole occur after the administration of DTP (diphtheria, tetanus, and pertussis) vaccines, either alone or in combination with OPV (oral polio vaccine). For this reason, DTP, especially the pertussis component, has been the target of numerous studies centered around its safety and efficacy.

This chapter provides an assessment of the major and minor risks of pertussis vaccination and emphasizes the importance of observing contraindications to immunization. Several studies are discussed which show the absence of a causal relationship between pertussis immunization and SIDS. The clinical disease of pertussis, the cost-effectiveness of continuing pertussis vaccination programs, and the development of the new acellular pertussis vaccine will all be discussed briefly in order to provide a context for the controversy currently surrounding pertussis immunization.

Pertussis

Pertussis (whooping cough) is an acute, highly communicable, epidemic bacterial disease of relatively long duration that usually strikes infants and young children. In Japan, pertussis is called "Hyakunichi-zeki," which means the cough persisting for one hundred days. The causative agent is *Bordetella pertussis*, a small,

nonmotile, gram-negative coccobacillus. The clinical disease is characterized by a paroxysmal, spasmodic cough that usually ends in a labored inspiration which creates the "whoop" from which its common name is derived. The incubation period is about one to two weeks, and the disease frequently lasts six or more weeks, divided into three stages: catarrhal, paroxysmal, and convalescent. It is a serious disease in children under age 2, carrying a 2% mortality rate before age one (71). Secondary bacterial infections are a frequent cause of complications.

Pertussis Vaccines

The development of a successful technology for the manufacture of heat-killed vaccines by Salmon, Smith, Pfieffer, Wright and other vaccine pioneers at the turn of the century paved the road towards the manufacture of an efficacious pertussis vaccine. The development of this vaccine was discussed in the first chapter. DTP vaccines were widely accepted in the United States in the late 1940's and became part of the recommended program of the Committee on Infectious Diseases of the American Academy of Pediatrics in 1947. Pertussis vaccination became mandatory in Japan in 1950, but was not adopted until much later in most of Europe. DTP did not become part of the national immunization program in Great Britain until 1957. In 1984 in the United States, there were

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71. Berkow R, ed. The merck manual of diagnosis and therapy. 14th ed. Rahway: Merck Sharp & Dohme Research Laboratories, 1982.

6,351,097 doses of DTP administered in the public sector, representing a very high public acceptance rate of the vaccine (72).

Adding to the controversy surrounding the safety of the pertussis vaccine are issues about its efficacy. The standard vaccine used in the United States and Europe is not 100% effective and does not provide lifelong immunity. Therefore, certain individuals will undertake the risk associated with the vaccine and still contract whooping cough. However, prior vaccination seems to lessen the severity of the disease as well as the complication rate. The best estimates report an efficacy of the United States whole-cell pertussis vaccine of 80% to 90% (73).

Descriptive Pertussis Epidemiology

The reported pertussis attack rate in the United States dropped from a stable level of about 200 per 100,000 population between 1925 and 1945, to about 50 per 100,000 population in 1955, and still lower to about 0.8 per 100,000 population in 1981. During that same time period, the mortality rate dropped from close to 10 per 100,000 population in 1925 to .008 per 100,000 population in 1981 (74). James Cherry writes that "Since there is no other known reason for the fall of pertussis attack rates in the United States, it appears that

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72. Centers for Disease Control. Adverse events following immunization: Surveillance report no. 2, 1982-84. Atlanta: Centers for Disease Control, 1986.

73. Fulginitti V. Immunization in clinical practice. Philadelphia: J.P. Lipincott Company, 1982.

74. Centers for Disease Control. Annual summary 1981: Reported morbidity and mortality in the United States. MMWR 1982; 30: 54.

vaccine use in the United States was responsible for the reduction in pertussis" (75).

Adverse Reactions to U.S. Whole-Cell Pertussis Vaccines

Adverse reactions to immunizations are not a new subject in the medical literature. There is a broad range of reactions associated with pertussis vaccination that begins with mild pain or redness at the site of injection and extends to serious, permanent neurological sequelae or even death. Doubts about the safety of the vaccine arose almost immediately with its first usage in 1913 (76) and reports of allegedly severe reactions were first published by Madsen in 1933 (77).

The Overall Magnitude of the Problem

During the period January 1, 1982 through December 31, 1984, the CDC received 3,861 reports of individuals who had suffered adverse events following immunizations administered by public health care providers severe enough to require medical attention. The drawbacks in the current reporting system were discussed in the previous chapter. Nevertheless, 2,600 (67%) of these persons had received DTP immunizations. Fifty-one percent had received OPV,

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75. Cherry JD. The epidemiology of pertussis and pertussis immunization in the United Kingdom and the United States: A comparative study. Current Problems in Pediatrics 1984; 14: 2-78.

76. Chase A. Magic shots. New York: Wm. Morrow & Co., 1982.

77. Madsen T. Vaccination against whooping cough. JAMA 1933; 101: 187-8.

which is usually administered at the same time as DTP, and 19% had received only DTP (78).

During the time span 1982-1986 there were 48 deaths that occurred within 30 days of vaccination in California. Twenty-five of these occurred after DTP/OPV administration, while 11 occurred after DTP alone. Twenty-seven of these deaths were Sudden Infant Death Syndrome (SIDS) or encephalopathy-related deaths in infants (79).

Less Serious Reactions

Since the minor reactions to pertussis immunization are not life-threatening and apparently very common, there are few good studies delineating them. Mc Comb and Trafton reported that 43-58% of pertussis vaccine recipients in 1950 had erythema at the injection site of 2.5 cm or more, and 9-14% had fever (80).

The Medical Research Council in Great Britain, while conducting the Final Report to the Whooping-Cough Immunization Committee, found either local, general, or both kinds of reactions in 85% of vaccine trial recipients visited 48-72 hours after their first immunization (81). Specific reactions were not otherwise classified.

78. Centers for Disease Control. Adverse events following immunization: Surveillance report no. 2, 1982-84. Atlanta: Centers for Disease Control, 1986.

79. compiled from unpublished CDHS data

80. McComb JA, Trafton MZ. Immune responses and reactions to diphtheria and tetanus toxoids, with pertussis vaccine, aluminum phosphate precipitated. N Engl J Med 1950; 243: 442-5.

81. Medical Research Council. Vaccination against whooping cough: The final report to the whooping-cough immunization committee of the

Such high frequencies of minor reactions have not been noted in all studies. No reactions were noted in 82% of 1,181 doses of DTP vaccine administered by Provenzano et al. in 1959 (82). However, the methods of evaluation were not described in this article. Similar results were obtained by Miller et al. (83) between 1972 and 1974 at the Epidemiological Research Laboratory in England. Eight hundred and ninety-seven doses of a single batch of DTP vaccine were administered, and, in almost every case, the children were seen by a nurse 24 hours after the injection and again 4 weeks later. Eighty-one percent of the injections produced no reaction, and another 12% were classified as "trivial." Unfortunately, this last category was not further delineated, and there was apparently no objective measurement of temperature.

Barkin and Pichichero (84) surveyed parents from all socioeconomic backgrounds attending four pediatric practices to obtain information about reactions to pertussis immunization in their children within the first 48 hours after injection. They received 1,232 completed questionnaires, representing a response rate of 89%. Reactions were classified as absent, mild, moderate, or severe and

medical research council and to the medical officers of health for Battersea and Wandsworth, Bradford, Liverpool, and Newcastle. Br Med J 1959; 1: 994-1001.

82. Provenzano RW, Wetterlow LH, Ipsen J. Pertussis immunization in pediatric practice and in public health. N Engl J Med 1959; 261: 473-7.

83. Miller CL, Pollock TM, Clewer ADE. Whooping-cough vaccination: An assessment. Lancet 1974; 2: 510-15.

84. Barkin RM, Pichichero ME. Diphtheria-pertussis-tetanus vaccine: Reactogenicity of commercial products. Pediatrics 1979; 63: 256-60.

grouped into three categories: temperature, behavioral changes, and local reactions. DTP administration was associated with some reaction in 93.0% of cases. Despite the use of antipyretics in over 65% of the children, fever was reported in 53.6% of all patients, with 4.2% spiking fevers greater than 102'F. Acute behavioral changes were noted in 81.8% of vaccine recipients, with 12.9% of children displaying prolonged screaming. Local reactions at the site of injection were noted in 72.2% of vaccinees. No encephalitis, seizures, or hospitalizations were reported.

Cody et al. (85) conducted by far the most extensive prospective study of reactions following pertussis vaccination. Over sixteen thousand (15,752 DTP and 784 DT) injections were given to children in the age range zero to six years who were then followed for 48 hours by home visits, telephone calls, or mail-in questionnaires. Despite the small number of DT injections, there were significantly fewer adverse reactions to DT than DTP, lending credence to the idea that the pertussis component of the triple vaccine is largely responsible for the frequency of reactions. The study noted at least one minor reaction in over 50% of the children immunized with DTP. The ratio of reaction rates associated with DTP and DT were as follows: local redness, 37.4%/7.6%; local swelling, 40.7%/7.6%; pain, 50.9%/9.9%; fever, 31.5%/14.9%; drowsiness, 31.5%/14.9%; fretfulness, 53.4%/22.6%; vomiting, 6.2%/2.6%; anorexia, 20.9%/7.0%; and persistent crying, 3.1%/0.7%. P values

85. Cody CL, Baraff LJ, Cherry JD, et al. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981; 68: 650-60.

registered <.0001 for all the local reactions. Similar levels of significance were achieved for all the systemic reactions as well, with the exception of persistent crying which was p< .0003.

More Serious Reactions

A host of more serious reactions has also been attributed to pertussis immunization. The list includes febrile and non-febrile convulsions, encephalopathies, permanent neurological damage, and SIDS.

Research seems to indicate a clear association between DTP immunization and encephalopathy. In an early study, Ström (86) reported retrospectively on 516,276 triple-vaccinated children in Sweden from 1959 to 1965. He noted neurological reactions to the vaccination in 167 cases: 3 with destructive encephalopathy, 80 with convulsions, 4 with hypsarrhythmia, 54 with hypotonic shock, 24 with uncontrollable screaming, and 2 with serous meningitis. These cases represented an occurrence of severe reactions of 1/3,100 vaccinated children, 75.5% of whom had received at least 3 doses of DTP.

Kulenkampff et al. (87) in 1974 presented case studies of 36 children seen in the previous 11 years who were believed to have suffered from neurological complications in the first 24 hours after

86. Strom J. Further experience of reactions, especially of a cerebral nature, in conjunction with triple vaccination: A study based on vaccinations in Sweden 1959-1965. Br Med J 1967; 575: 320-3.

87. Kulenkampff M, Schwartzman JS, Wilson J. Neurologic complications of pertussis inoculation. Arch Dis Child 1974; 49: 46-9.

pertussis inoculation. While the authors admitted that their data was incomplete and that causation was being implied merely from a clustering of cases, their findings were sufficiently alarming to cause the decrease in public vaccine acceptance in England in the following years that was discussed in the last chapter.

In response to the decreasing immunization rate, increasing pertusssis rate, and public pressure, during the period 1976-79 in Britain the National Childhood Encephalopathy Study (NCES) undertook the task of establishing the true relationship between pertussis vaccine and neurological disorders. The study registered all children in England with the onset of acute neurological illnesses (including encephalitis and encephalopathy, prolonged or complicated convulsions, infantile spasms, and Reye's syndrome) to the study group, each case of which was compared to two controls. Lasting neurological damage was classified as causing a neurologic handicap one year after symptom onset. Some 1,180 cases of serious neurological disorders satisfied the study criteria and were registered.

Miller et al. (88) reviewed the first 1,000 cases from this large case-control study. Thirty-five cases, 32 of whom had no previous neurological abnormalities, had received DTP immunization within 7 days prior to disease onset. The remaining 965 had not. The relative risk of a notified child having had pertussis immunization seven days prior to the onset of neurological disease was 2.4 (p<0.001). The risk

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88. Miller DL, Ross EM, Alderslade R, et al. Pertussis immunisation and serious acute neurological illness in children. Br Med J 1981; 282: 1595-9.

was greatest for immunizations within 72 hours and in children with severe convulsions or encephalopathies. One year later, 2 had died, 9 were developmentally delayed, and 21 were completely recovered. The attributable risk of a serious neurological disorder after pertussis immunization was estimated at 1/110,000 immunizations (95% confidence limits 1/360,000 to 1/44,000) and that of lasting neurological damage was estimated at 1/310,000 immunizations (95% confidence limits 1/5,310,000 to 1/54,000).

In their prospective study, Cody et al. noted 9 children who developed convulsions following DTP immunization, and 9 who developed hypotonic hyporesponsive episodes. None of the 18 children had sequelae following these reactions (89).

Contraindications to Pertussis Immunization

Careful evaluation of other potential risk factors in the cases presented in the studies above reveals an astonishing fact. Nearly 50% of the serious neurological complications observed in the NCES occurred in children with one or more contraindications to pertussis immunization. Furthermore, Kulenkampff's research group reported that as many as a third of their cases had valid contraindications to pertussis immunization.

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89. Cody CL, Baraff LJ, Cherry JD, et al. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981; 68: 650-60.

Stetler et al. (90) better delineated the risks of subsequent adverse neurological reactions to DTP immunizations from previous neurological conditions. Data on 2,062 reports of adverse events following DTP immunization from the CDC were analyzed. Children who experienced a neurological adverse reaction had a 7.2 times higher risk for personal history of convulsions (95% confidence limits 4.5 to 11.5) and a 4.5 times higher risk for a family history of convulsions (95% confidence limits 3.1 to 6.7) than did children who had non-neurological adverse events following DTP injection.

Baraff et al (91) found in a study of 1,241 children immunized with second or third doses of DTP that both local and systemic reactions within 48 hours were significantly more frequent if similar reactions had occurred following primary (first dose) DTP immunization. They found rates of local reactions (no prior reaction/prior reaction) of: local redness or swelling greater than or equal to 2.5 cm, 12.5%/25.5% (p<.001); local swelling greater than or equal to 2.5 cm, 16.8%/29.0% (p<.001); and local pain, 37.4%/56.4% (p<.001). The rates of systemic reactions as a function of previous reactions yielded similar results (no prior reaction/prior reaction): drowsiness, 24.9%/42.8% (p<.001); fretfulness, 47.5%/64.7% (p<.001); vomiting, 4.8%/11.2% (p=.0084); anorexia, 16.0%/26.3% (p=.001); fever of at least 38'C, 37.6%/68.5% (p<.001); and persistent crying, 2.6%/4.5% (p=.3557).

90. Stetler HC, Orenstein WA, Bart KJ, et al. History of convulsions and use of pertussis vaccine. J Pediatrics 1985; 107: 175-9.

91. Baraff LJ, Cherry JD, Cody CL, et al. DTP vaccine reactions: effect of prior reactions on rate of subsequent reactions. Dev Biol Stand 1985; 61: 423-8.

These data underscore the importance of observing the contraindications to immunization. In the state of California current contraindications recommended by the CDHS are provided to all public vaccine administrators in an easy-to-follow one page poster format. Contraindicative to a first dose of any vaccine is any condition of obviously acute illness (i.e. fever and/or appears very sick). Contraindications to either a first or subsequent dose of DTP are an evolving neurologic disorder (e.g. uncontrolled epilepsy) or a recently (<6 mos.) developed neurologic disorder (e.g. recent convulsions), or a serious reaction to a prior DTP dose (e.g. fever >105'F within 48 hrs.; convulsions within 3 days; persistent, inconsolable crying for > 3 hrs. or unusual high-pitched screaming or crying within 48 hrs.; hypotonic-hyporesponsive episode; encephalopathy within 7 days; or an anaphylactic reaction).

SIDS and DTP

A number of SIDS deaths within 30 days of DTP vaccination in California was already mentioned. Evidence of a temporal relationship between SIDS and DTP is also seen at the national level (92). During 1982-84 there were 42 SIDS and 25 non-SIDS post-vaccination deaths reported to the CDC. All of the reported SIDS deaths occurred after DTP/OPV or DTP alone except for one, which occurred after IPV alone. A cause of death unrelated to the vaccines was determined in 56% of the non-SIDS deaths.

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92. Centers for Disease Control. Adverse events following immunization: Surveillance report no. 2, 1982-84. Atlanta: Centers for Disease Control, 1986.

In order to help assess the risk of SIDS from DTP immunization, a mathematical model to predict the number of SIDS deaths that would occur annually by chance alone within 24 hours of DTP vaccination was designed by the CDC and the NIH. This model assumed a national SIDS rate of 1.46 SIDS deaths per 1,000 live births (derived from National Center for Health Statistics data); 3.6 million live births per year in the United States; that each infant receives three doses of DTP from five to fifty-two weeks of age; and uses the Norwegian study by Solberg (93) for a background incidence of SIDS in the absence of vaccination.

Final calculations predicted that between 18.2 and 30.8 SIDS deaths in the U.S. should occur each year by chance alone within twenty-four hours of receipt of public sector DTP vaccinations. Similarly, between 36.3 and 61.5 SIDS deaths should occur within forty-eight hours of public sector DTP vaccinations each year. These figures are higher than the average reported to the CDC's monitoring unit of 7 annual SIDS deaths occuring within forty-eight hours after immunization (94).

There are several scenarios which could explain this finding. Under-reporting of SIDS by health care providers may be one factor, but may not account for the entire difference. A multi-center

93. Solberg LK. DTP vaccination, visit to child health center, and sudden infant death syndrome (SIDS): Evaluation at DTP vaccination. NIH-85-152 (NIH Library Translation).

94. Centers for Disease Control. Adverse events following immunization: Surveillance report no. 2, 1982-84. Atlanta: Centers for Disease Control, 1986.

cooperative NIH SIDS study (95) reported that infants who had died from SIDS were significantly less likely (p<.001) to have ever received DTP than were matched controls. This may indicate that there is some other factor in the social or biological environment of some of the children who will die of SIDS that makes them less likely to be vaccinated. The NIH therefore concluded that "DTP immunization is not a factor in the etiology of SIDS." Similarly, the Norwegian study from which the background data for the model was drawn concluded that "DTP immunization is not associated with SIDS."

The absence of a causal relationship between SIDS and pertussis immunization is also supported by the observations of the Immunization Practices Advisory Committee of the CDC (96). In the United States, the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months of age. The peak age-incidence for SIDS is 2 to 4 months. In countries where the pertussis vaccination series is not started until 6 months of age, the age distribution of SIDS cases is the same as that in the United States.

Acellular Vaccine Development

95. Hoffman HJ, Hunter JC, Damus K, et al. Diphtheria-tetanus-pertussis vaccination and sudden infant death: Results of the NICHD cooperative epidemiological study of sudden infant death syndrome (SIDS) risk factors. In: 17th immunization conference procedings, May 18-19, 1982. Atlanta: Centers for Disease Control, 1982.

96. Immunization Practices Advisory Committee, Centers for Disease Control. Diphtheria, tetanus, and pertussis: Guidelines for vaccine prophylaxis and other preventive measures. Ann Intern Med 1981; 95: 723-8.

In an effort to reduce the frequency and severity of reactions to pertussis vaccine, research has been undertaken to develop a safer vaccine. One of the more recent advancements in pertussis immunization technology is the development of an acellular vaccine by the Japanese, over 20 million doses of which have been administered in Japan since 1981 (97). Testing of the new vaccine shows that febrile responses for the acellular vaccine were significantly lower than those for the whole-cell pertussis vaccine.

Of three manufacturer's lots of acellular vaccine tested in Japan, febrile responses were noted respectively in only 2.6%, 1.2%, and 2.5% of vaccinees. This represents over a 15-fold decrease from the antigens used in Cody's study. While the sample size in the Japanese study was only 115 children, these results are most promising, especially when it is considered that no serious reactions were observed during the trial (98).

Some trials of this vaccine have also been conducted in the United States. Anderson et al. (99) administered acellular pertussis vaccine to 3 groups of 20 children each. No reactions occurred that were serious enough to contraindicate subsequent doses, although older children (4 to 6 years of age) had significantly more local

97. Noble GR, Bernier RH, Esber EC, et al. Acellular and whole-cell pertussis vaccines in Japan. Report of a visit by U.S. scientists. JAMA 1987; 257: 1351-6.

98. Aoyama T, Hagiwora S, Murase Y, et al. Adverse reactions and antibody responses to acellular pertussis vaccine. J Pediatrics 1986; 109: 925-30.

99. Anderson EL, Belshe RB, Bartram J, et al. Clinical and serological responses to acellular pertussis vaccine in infants and young children. Am J Dis Child 1987; 141: 949-53.

redness and swelling and fever than did younger children or infants. Pichichero et al. (100) administered either acellular or whole-cell pertussis antigens combined with DT to 120 children who had previously been immunized with three doses of whole-cell DTP preparations. Recipients of the whole-cell vaccine were significantly more likely to have a fever than were recipients of the acellular preparation (p=.00008). The peak difference occurred at 6 hours post-immunization. Local swelling, redness, warmth, and tenderness at the injection site were also significantly more frequent following whole-cell immunization than acellular immunization. No serious reactions were noted in either group.

Lewis' group (101) found similar results in a double-blind study of sixty 18- to 24-month-old children who were given either acellular or whole-cell pertussis as the fourth DTP vaccine dose. Reactions over the first 48 hours were significantly less common in the acellular recipients (whole-cell DTP/acellular DTP): fever, 85%/5%; redness, 70%/12.5%; tenderness, 100%/22.5%; swelling, 35%/10%; fretfulness, 70%/12.5%; anorexia, 35%/2.5%; and vomiting, 10%/0%.

100. Pichichero MC, Badgett JT, Rodgers GC Jr, et al. Acellular pertussis vaccine: immunogenicity and safety of an acellular pertussis vs. a whole cell pertussis vaccine combined with diphtheria and tetanus toxoids as a booster in 18- to 24-month old children. Pediatr Infect Dis J 1987; 6: 352-63.

101. Lewis K, Cherry JD, Holroyd HJ, et al. A double-blind study comparing an acellular pertussis-component DTP vaccine with a whole-cell-pertussis component DTP vaccine in 18-month-old children. Am J Dis Child 1986; 140: 872-6.

In an earlier study, Lewis et al. (102) monitored 36 four to six year-old children for 48 hours following the administration of acellular DTP. All children had received three previous doses with whole-cell DTP. Redness and tenderness were both noted in 50% of recipients, while swelling was noted in 41%. Fever greater than or equal to 38'C was seen in only 3% of vacinees. Other general reactions included drowsiness (17%), fretfulness (14%), anorexia (11%), and vomiting (6%).

The acellular vaccine has also proven to be equally efficacious to the more dangerous standard vaccine. In a survey of secondary cases in 283 household contacts, attack rates in children 0 to 6 years of age were 73.1% in unimmunized children, 15.0% in those fully immunized by whole-cell vaccines, and 15.4% in those immunized with acellular vaccines. The efficacy of Japanese acellular pertussis vaccine was 79% and was not significantly different from that of the whole cell vaccines typically used in the United States (103).

Unfortunately, none of the studies described above have included sample sizes or study designs sufficient to detect the incidence of serious neurological adverse outcomes to the new acellular vaccine. A prospective study, similar in scale to Cody's whole-cell pertussis study, must be performed in this country before the acellular vaccine is adopted for use. It seems that Japan has

102. Lewis K, Cherry JD, Baraff LJ, et al. An open study evaluating the reactogenicity and immunogenicity of a DTP vaccine containing an acellular pertussis component in four to six year old children. Dev Biol Stand 1985; 01: 563-9.

103. Aoyama T, Murase Y, Kato T., et al. Efficacy of an acellular pertussis vaccine in Japan. J Pediatrics 1985; 107: 180-3.

been fortunate in that no disastrous consequences have arisen from their premature dispersion of the new vaccine.

The development of this acellular vaccine relies on the concept first postulated by Pasteur that only certain components of a pathogen are necessary to induce immunity. The high incidence of febrile reactions to the U.S. whole-cell vaccine is thought to be attributable to the presence of endotoxin, a pyrogenic substance in the bacterial cell wall. Unlike many other bacterial vaccines which are composed of only certain antigens belonging to the infectious disease agent (e.g. polysaccharides from the pneumococcal capsule), pertussis vaccine contains the entire bacterial organism. Bacteria are grown as Phase I organisms chemically killed with phenol or formalin. The final vaccine preparation also contains a preservative, frequently a mercurial compound. The low febrile response rate following acellular immunization is attributed to the fact that the acellular vaccine, since it does not include the entire bacterium, does not include endotoxin. The components of the acellular vaccine that induce immunity are filamentous hemagglutin and the pertussis toxin.

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vaccine was 79% and was not significantly different from that of the whole cell vaccines typically used in the United States (104).

Cost-Benefit Analysis

With predicted rates of post-vaccination encephalopathy following pertussis immunization such as those provided by the NCES, and the imperfect efficacy of the vaccine, is it worth the risk to immunize our children? One way of approaching this question is through a structured decision analysis study. Several authors have done mathematical cost-benefit analyses weighing the risks of foregoing pertussis immunization in the community. One conclusion continues to result from these analyses: that the benefits outweigh the costs, and that pertussis immunization should be continued at high levels with very careful attention to contraindications in certain patients.

Koplan et al (105) used decision analysis to predict that there would be a 71-fold increase in pertussis cases and almost 4 times the number of pertussis-related deaths per cohort of one million children in the absence of current immunization programs. However, with an immunization program, the authors predicted 0.1 cases of pertussis-associated encephalitis and 5.0 cases of post-vaccination encephalitis compared to only 2.3 cases of encephalitis associated with naturally occuring pertussis in the absence of a vaccination program. The

104. Aoyama T, Murase Y, Kato T., et al. Efficacy of an acellular pertussis vaccine in Japan. J Pediatrics 1985; 107: 180-3.

105. Koplan JP, Schoenbaum SC, Weinstein MC, et al. Pertussis vaccine-- An analysis of benefits, risks, and costs. N Engl J Med 1979; 301: 906-11.

authors concluded that the benefits of current (1979) pertussis immunization programs would continue to outweigh the costs until the incidence of post-vaccination encephalitis increased eight times.

In a more recent report, Hinman and Koplan reanalyzed the costs and benefits of pertussis vaccination in a hypothetical cohort of one million children from birth to six years of age. Making very conservative estimates not including indirect costs such as those associated with death or lost wages, and assuming only an 80% vaccine efficacy with no protective effect until the third dose, they estimated that the costs to the community are reduced by 82% by a vaccination program. The ratio of overall costs without a program to those with a program were estimated at 5.7:1. The authors concluded that "Until improved vaccines are available, continued use of our present vaccines, with careful attention to possible contraindications, seems the only prudent course to follow" (106).

It is worth noting that two issues deeply imbedded in current vaccine policy can affect these cost-benefit ratios. The spiraling costs of vaccines tend to drive the cost-benefit ratios closer to parity, while the development of safer vaccines tends to increase the benefits associated with community vaccination programs.

Conclusion

The controversy surrounding the safety and efficacy of pertussis immunization continues today, both in the United States

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106. Hinman AR, Koplan JP. Pertussis and pertussis vaccine: Reanalysis of benefits, risks, and costs. JAMA 1984; 251: 3109-13.

and abroad. Careful review of the literature suggests that, while it is not causally linked to the Sudden Infant Death Syndrome, pertussis immunization does carry with it a definite risk for permanent neurological damage, as well as many more minor adverse reactions.

Policy Implications

Despite the risks detailed above, the disastrous consequences of declining pertussis immunization rates in England and Japan coupled with structured decision analysis illustrates the necessity of continued community vaccination programs. Although the data upon which we must base public policy decisions are generated from often imperfect studies, it appears that encephalitis and the rare serious neurological sequelae associated with vaccination are an unpleasant but necessary trade-off for the avoidance of an even greater morbidity and mortality due to naturally occurring pertussis infection in the absence of community immunization efforts.

However, all efforts must be made to decrease the risks associated with pertussis immunization. Several studies have been presented here which demonstrate the importance of observing valid contraindications to either primary or subsequent doses of DTP injections.

In addition, the acellular pertussis vaccine tentatively seems less likely to cause adverse reactions while providing immunity equal to that of the whole-cell vaccine. Large-scale controlled studies should be performed immediately in this country in order to assess the true risks associated with this vaccine more adequately.

If it indeed proves to be a safer vaccine, it should be adopted for use in this country as quickly as possible.

Chapter Five

VACCINE POLICY AND REGULATION

Introduction

With the spread and development of variolation and vaccination in the Western world also came the development of laws and regulations controlling these potentially very useful but dangerous practices. This chapter will provide a historical overview of the history and development of international, state, and federal laws regulating vaccination practices. The current environment in which vaccine policy is now formulated will also be discussed. Included in this discussion will be issues of vaccine cost-effectiveness, the rising costs of vaccines in the face of increasing legal liability, the unavoidable risks involved with vaccination, legal and ethical issues surrounding vaccination, new plans and payment schemes for vaccine-related injury compensation, and modern vaccine research and development efforts.

Vaccine Policy, Regulation, and Licensure

Policies regulating immunization practices in Europe arose almost immediately after the introduction of variolation. For almost three centuries these policies have centered around increasing governmental control and regulation of immunization practices. As early as 1722, soon after Maitland's experiments, James Jurin, Secretary of the Royal Society of physicians in England requested that "All persons concern'd in the Practice of inoculating the Small Pox, are desir'd to keep a Register of the Names and Ages of every Person inoculated, the Place where it is done, the Manner of the Operation, the Days of sickening and of the Eruption, the Sort of Small

Pox that is produc'd, and the Event" (107). This was an admirable attempt to maintain accurate records in an effort to help evaluate the risks and benefits of variolation practices. Some of the data generated by this reporting system was discussed in previous chapters.

Early variolation efforts in Europe were nearly always voluntary. In fact, they could often be afforded only by the rich. The first evidence of compulsory inoculation can be found in London in 1743 (108). In that year, the board of the Foundling Hospital ordered that all children already in the hospital and any over the age of three who were admitted and had not yet had the disease, would be inoculated against smallpox. By 1746, a year in which the incidence of smallpox in London reached its highest level in a decade, public efforts were being made to increase variolation activities in London. A special hospital had been founded for the treatment of smallpox victims, attached to which facility were additional facilities for the inoculation of the poor. By 1754, variolation was officially recommended by the Royal College of Physicians.

Following Jenner's breakthrough in 1798, the use of cowpox vaccine quickly supplanted variolation. Approximately 100,000 persons had been vaccinated throughout the world by the year 1800 (109). Despite the fact that an estimated 70% of children in certain

107. Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 234.

108. Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 239.

109. Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 27.

parishes in England in 1840 were vaccinated, the British Parliament did little to regulate vaccination until well into the nineteenth century. However, other European governments implemented regulations much more expeditiously (110,111,112).

In 1801 the King of Denmark enforced regulations providing for the free vaccination of soldiers and their families, sailors, students in public schools, and the poor. Nine years later, vaccination was made legally compulsory. Vaccination became part of a nationally recommended policy in Austria in 1801, and was made compulsory in Bavaria in 1807.

As early as 1818 in Wirtemburgh, a country which is now part of Germany, the King issued enactments strictly promoting the use of vaccination. "Every child must be vaccinated before it has completed its third year, under a penalty annually levied on its parents so long as the omission continues; and if the operation fail, it must be repeated every three months until a third trial. No person to be received into any school, college, or charitable institution; be bound apprentice to any trade; or hold any public office who has not been vaccinated" (113). This law also included sensible public health measures such as provisions for outbreak control, with a clause

110.   Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 278-282.

111.   Baron J. The life of Edward Jenner...with illustrations of his doctrines and selections from his correspondence. London: H. Colburn, 1827: 475-478.

112.   Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 25-39.

113.   Dixon CW. Smallpox. London: J. & A. Churchill, Ltd., 1962: 278.

requiring the immediate vaccination of susceptibles during epidemics.

The policy history of vaccination in England is well-delineated, and comprehensive, since the majority of regulation took place at the national level. State support was given to vaccination projects and research in England from 1807 on, and by 1825 it is estimated that nearly half of the children born in the large towns of Britain were being vaccinated. However, the first legislation passed with the intent to diffuse the practice of vaccination was not passed until 1840, seventeen years after Jenner's death. This act entitled, but did not require, the civil guardians in England and Wales to contract with registered medical practitioners to provide free vaccination for the local indigent population.

The Second Vaccination Act in 1853 did, however, make smallpox vaccination compulsory. It also outlawed the practice of variolation. The law levied quite strict fines on those parents who did not comply with the regulations for their children, but was not strictly enforced until 1871, in which year 23,000 deaths occurred in England from a major smallpox epidemic. The average death rate from smallpox was 223 per million during the period 1854-1871, but fell to 89 per million between 1872 and 1891 when compulsory vaccination was better enforced (114).

In 1867, another act was passed which, rather than regulating the recipients of smallpox vaccine, regulated the vaccine

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114. Parish HJ. A history of immunization. London: E. & S. Livingstone, Ltd., 1965: 30.

administrators. This law required a certificate of competency of those practitioners wishing to vaccinate their patients and stayed in effect until it was repealed by the National Health Service Act in 1946.

In 1896 in London, the compulsory vaccination laws were modified in order to add a provision for conscientious objectors. These C.O.'s had to prove to the local justices that their consciences were indeed bothered, so the rate of exemptions in different counties varied with the leniency and sympathy of these state representatives until 1907, when the law was amended. At that time a statutory declaration by the parents became sufficient for exemption of their children.

Arm-to-arm vaccination by public vaccinators had been outlawed in 1896, but remained legal for private physicians until 1903, when the use of calf lymph became mandatory for all practicioners. These changes greatly reduced the risk of syphilis transmission inherent in the arm-to-arm method.

The new smallpox vaccine was the impetus for legislation in the United States as well as Europe. In Massachusetts in 1810, seven years after New York had started publicly funding vaccination efforts, the state authorized individual towns to raise money to cover the expense of vaccination. In Maryland, James Smith, who was one of the first American physicians to administer the new vaccine, was appointed State Vaccine Agent to both Virginia and Maryland. Later Congress appointed him the National Vaccine Agent, a position which entitled him to mail vaccine material anywhere in the country

postage free (115).

The Vaccine Act of 1813 was the first federal law to regulate drug distribution (116). This act, which authorized the President to name a federal agent to "preserve the genuine vaccine matter, and to furnish the same to any citizen" who requested it, was repealed in 1822 when Congress redelegated vaccine regulation to local authorities. No federal law analagous to the British statutes requiring vaccination of all citizens was ever passed in the United States.

Rather, regulation of vaccination against the smallpox remained largely at the state level, until eradication of the disease made vaccination unnecessary. As a result, the policy history of vaccination in this country is fragmented and difficult to trace. This trend has continued to the present time, and states vary widely in the legal requirements concerning compulsory vaccination against several infectious diseases. These state laws, however, have in common the fact that they are usually enforced at the time of first school entry for local children.

Even before smallpox vaccination was made mandatory, however, its use was almost universal in certain states, aided by organized efforts of local groups of administrators and physicians (the earliest Boards of Health). Unfortunately, smallpox remained endemic in those cities or states with large unimmunized populations

115. Rothstein WG. American physicians in the 19th century. Baltimore: Johns Hopkins University Press, 1972: 31.

116. Hutt PB. Investigations and reports respecting FDA regulations of new drugs. Clin Pharmacol Ther 1983; 33: 527-548 and 674-687.

well into the latter half of the nineteenth century. In 1858 in New York, there were over 400 deaths from smallpox. It was lamented by New Yorkers that only 413 deaths had occured in Boston during the six years concluding in 1854 since systematic vaccination had been established in that city (117).

By 1862, the state of Rhode Island had made vaccination against the smallpox compulsory, and no child was admitted to public school without a certificate of vaccination. In 1872, the New York Health Board finally recommended compulsory vaccination to the legislature of that state. A recent epidemic of smallpox was blamed on an increasing incidence of unvaccinated children among the poorer classes as well as increasing numbers of unvaccinated immigrants. It was estimated that 35,000 unvaccinated infants were being born each year in New York City. The Board urged that "If no child were allowed to pass its sixth month without being properly vaccinated, the materials for small pox would be so limited in amount and so widely scattered that only isolated cases could occur." The Board also wisely recommended that a group of vaccinators be established in order to administer the vaccine free of charge to the indigent population (118).

The further development of U.S. vaccine policy did not occur in a vacuum. A pattern of increasing regulation and control of food and drug products occurred at a time in this country during the latter half of the nineteenth and begining of the twentieth centuries when

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117.   The New York Times. Dec. 27, 1858.

118.   The New York Times. Dec. 19, 1872.

government regulation was expanding rapidly in all sectors.

The first temporary Board of Health was established in Massachusetts in 1799 in response to a cholera outbreak and was headed by Paul Revere. A more permanent board was organized in New York City in 1866, and the first effective state board was developed in Massachusetts in 1869. By 1909, all states had organized health boards.

The first Federal efforts to regulate industry sprung from public health concerns in 1838 in response to a sequence of catastrophic steamboat boiler explosions. This legislation, which was added to in 1852, established maximum pressure standards and provided for regular testing and inspection of the boilers. However, it was not until 1887, with the passage of the Interstate Commerce Act and the establishment of the Interstate Commerce Commission, that the Federal government moved to regulate an industry that was really vital to the nation's economy-- the railroads.

The federal policing mode of the Progressive reform era came to a peak during Theodore Roosevelt's second term in office. In 1906, in short order, the Pure Food and Drug Act, the Meat Inspection Act, and the Hepburn Act (which amended the Interstate Commerce Act) were all passed into law. However, these laws were not, according to Rabin, the result of a political movement. Rather, each of them "was initiated by distinct coalitions of political interests...[in] a political climate that was receptive to a variety of particularized complaints that the market needed to be policed with

greater vigor" (119). In particular, the passage of the Pure Food and Drug Act has been attributed to the decade-long lobbying efforts of Harvey Wiley, then head of the Bureau of Chemistry in the U.S. Department of Agriculture. He campaigned for the regulation of mislabeling of food products and patent drug products.

While a prevailing attitude of Social Darwinism weakened political efforts aimed at social welfare during the late nineteenth century, public health legislation was the major exception. The number of health laws, mostly at the state level, grew dramatically between 1850 and 1900. These laws largely governed the quality of food and water, but extended into the regulation of drugs and other therapeutics. In fact, public health measures had gained such momentum that guilds as diverse as horseshoers and barbers used the protection of the public health as a basis to enroll neutrals in the legislature and convince judges that the public interest was at stake when they tried to pass protectionist laws (120).

Quarantine laws had existed in Europe since the fourteenth century and in America since early Colonial times, but the laws became increasingly strict and elaborate in the nineteenth century. In 1820, New York established quarantine laws that divided ships into classes depending on their perceived danger and dictated the differential fumigation of these ships. Congress did not raise objections to these laws, even when they eventually interfered with

119.   Rabin RL.   Federal regulation in historical perspective.   Stanford Law Review 1986; 38: 1189-1326.

120.   Friedman, LM.   A history of American law.   2nd ed.   New York: Simon & Schuster, Inc., 1985: 439-66.

interstate commerce.

The state of Massachusetts adopted the first general law against the adulteration of food in 1784 (121). By 1889, twenty-three states had laws prohibiting the adulteration of drugs. In that same year, Minnesota passed legislation outlawing the sale of cigarettes and tobacco to children under the age of sixteen.

In New York City, sound public health measures such as the use of diphtheria antitoxin, the treatment of tuberculosis as an infectious disease, a permit system for milk distribution, tenement health inspection, and medical supervision in the schools drastically improved the health of the populus, especially the infants and children. The infant mortality rate in Massachusetts dropped from 161.3 per 1,000 in 1880-1884 to 141.1 per 1,000 in 1900-1904 (122).

It is interesting to note that, in the absence of a strong underlying movement, many of these state and federal laws were not well enforced or lacked the power they needed to be effective. For instance, the Meat Inspection Act had no provision for seizure of spoiled goods or the imposition of criminal penalties. Removal of the government stamp of approval was the extent of punishment. In the United States versus Johnson, the Court construed the Pure Food and Drugs Act to prohibit only misstatements of the ingredients of a drug

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121. Hayes AH. Food and drug regulation after 75 years. JAMA 1981; 246: 1223-7.

122. Keller M. Affairs of the state: Public life in late 19th century America. Cambridge: Belknap Press of the Harvard University Press; 1977: 500-502.

and not misstatements regarding the curative properties of drugs (123).

Friedman states that, while there is no question about the number of health laws that were passed between 1850 and 1900, their impact is another question. "In most cases, the state did little more than place people's interests or passions on the record. The record suggests little real control over the quality of the products, even food" (124). Consumers and consumer advocates were demanding protection at a rate greater than administrative mechanisms for enforcement could match.

Regardless of the level of enforcement of these numerous state laws, including those making vaccination compulsory, they were met with certain resistance by those who felt that they infringed on personal freedom to an unacceptable extent. However, the police power of the states with respect to public health was upheld by the U.S. Supreme Court in the landmark Jacobson v. Massachusetts decision. The state of Massachusetts had made vaccination compulsory in February of 1902, but on July 17, 1902, Mr. Jacobson refused to be vaccinated. He believed that vaccination may be dangerous to him, and that the U.S. Constitution protected his right to choose his own fate. The Supreme Court ruled that "The liberty secured by the Constitution of the United States to every person within its jurisdiction does not import an absolute right in each

123. Rabin RL. Federal regulation in historical perspective. Stanford Law Review 1986; 38: 1189-1326.

124. Friedman, LM. A history of American law. 2nd ed. New York: Simon & Schuster, Inc., 1985: 439-66.

person to be, at all times and in all circumstances, wholly freed from restraint. There are manifold restraints to which every person is necessarily subject for the common good" (125). In accordance with the Massachusetts law, Mr. Jacobson was fined five dollars for his refusal to comply with vaccine laws. However, more importantly, state laws requiring compulsory vaccination have consistently been deemed constitutional since that first decision.

One other form of market regulation burgeoned during the post-Civil War period: licensing. The medical, pharmacy, and dental fields all became heavily licensed at the state level. The manufacture of vaccines fell under this form of regulation at the Federal level. The development of vaccine licensing procedures is nicely summarized in a report by the Institue of Medicine (126).

The Virus-Toxin Act was passed by Congress in 1902 following the death from tetanus of 13 children in St. Louis who had been immunized with antitoxin for diphtheria that had been prepared in a horse that shortly thereafter died of tetanus. This act authorized the Hygenic Laboratory of the Public Health Service to inspect manufacturing establishments, issue and revoke licenses, and otherwise ensure the safety and efficacy of vaccines and antitoxins. The process was overseen by a board under the Department of the Treasury.

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125. Childress J, King P, Rothenberg K, et al., eds. BioLaw: a legal and ethical reporter on medicine, health care, and bioengineering, Vol. 1. Frederick, MD: University Publications of America, 1986: 29-49.

126. Institute of Medicine. Vaccine supply and innovation. Washington, D.C.: National Academy Press, 1985: 16-18.

Thirteen manufacturers of biologics had been licensed to produce one or more vaccines for use in the United States by 1904, and the number had reached 41 by the year 1921. Interestingly, in 1986 only 12 commercial manufacturers (five of which do not produce vaccines in the United States), two state laboratories, and one university held licenses.

Responsibilities for licensing were later transferred to the National Microbiological Institute of the National Institutes of Health (NIH) as the 1902 act was incorporated into the Public Health Service Act of 1944. In the 1950's the Division of Biologics Standards was formed at the NIH from the old Public Health Service Hygenic Laboratory, and in 1972 administration of this division was transferred to the Food and Drug Administration (FDA).

Today, the Office of Biologics Research and Review (OBRR) of the FDA oversees the production and testing as well as the standards and licensure requirements of new vaccines. If a manufacturer wishes to study a new vaccine in humans, permission must be sought from the OBRR and a Notice of Claimed Exemption for Investigational New Drug (IND) must be filed. The IND includes information about the chemical composition and manufacture of the drug, results of all preclinical investigations, a protocol for the proposed clinical investigation, information on the experience of the clinical investigators, a statement of accordance with the requirements of Human Subjects Protection Committees, and an agreement to submit annual progress reports. The FDA has 30 days from the date of IND submission to approve or deny the application. The IND sponsor may also proceed with clinical studies in the event of absence of comment

from the FDA within the 30-day review period (127).

All IND vaccines must undergo three sequential phases of clinical testing. Phase I and Phase II trials establish the efficacy of the vaccine in question and include controlled studies that attempt to determine the safety of the vaccine. Phase III trials are essentially similar but use larger sample sizes than Phase II trials and verify that the acceptable benefit to risk ratios generated from earlier studies persist under conditions of anticipated usage. It is important from a policy standpoint to note that there are no specific Federal guidelines for the development of vaccines. They simply fall under the rubric of new drugs and biologics.

If the product promises to be profitable after these three testing phases, the IND sponsor files a license application with the OBRR. After reviewing the research regarding the safety and efficacy of the vaccine trials, the OBRR either grants or denies the license. Both vaccine manufacturers and every vaccine on the market require a license. After licensing, the OBRR encourages continued surveillance of vaccine recipients since the number of individuals who receive trial doses before full licensure is often too small to detect the rare adverse reactions associated with vaccines. Vaccine development needed to protect military personnel from unusual, mostly tropical diseases is overseen by the Department of the Army.

Once a vaccine has been marketed, it is usually administered according to a dosage schedule provided by one of several advisory

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127   American Medical Association. Drug Evaluations. 6th ed. Chicago: The American Medical Association, 1986: 8-12.

groups in the United States. The Immunization Practices Committee of the U.S. Public Health Service, the Committee on Infectious Diseases of the American Academy of Pediatrics, and the Committee on Immunization of the council of Medical Societies, American College of Physicians all have published recommendations for vaccine use.

Ethical, Policy, and Legal Issues Surrounding Vaccines: Compensation for Adverse Events Following Immunization

While the licensing procedures may seem straightforward, there are several important issues surrounding publicly mandated vaccination programs that form an intricate web of complicated public policy questions. Vaccination plays an important role in protecting both the individual and the society as a whole. A successful public vaccination program will result in disease immunity in the individuals who are immunized. But, by reducing the number of susceptible people in the populace of a community, it will also provide a social good by reducing the risk of epidemic for everybody in the community.

The etiologic agents of most infectious diseases require a certain number of susceptible individuals in a population in order to transmit in an epidemic manner. The concept of reducing the risk of epidemic diseases by decreasing the number of susceptible individuals below this critical point is referred to as herd immunity. An immunity rate of about 80% of the individuals in a community, either through the consequences of natural infection or immunization, is sufficient to prevent most epidemic diseases. In a community such as the United States, where a naturally acquired

disease such as pertussis has become rare, the finite risk inherent in each vaccination is borne by the individual, but the benefit is reaped by society as a whole.

Not all publicly mandated vaccines can induce herd immunity. For instance, no herd immunity results from tetanus vaccination since the vaccine induces immunity against only the toxin and not the micro-organism that produces the toxin.

The fact that the risk of vaccination is borne mainly by the individual gives rise to several interesting legal and ethical question. Most vaccines are given to young children under the age of six. Similarly, most human vaccine trials are performed on young children. Can those people who are undertaking the risks of vaccination therefore give "informed consent?" Does the state have the right to legally force these children to undertake risk in the absence of this informed consent?

One approach, other than legal paternalism, frequently taken to advocate this right is the use of cost-effectiveness analysis. These analyses usually demonstrate the substantial economic benefits derived from successful community immunization programs. Recent studies have estimated that measles vaccination resulted in a net savings of $5.1 billion dollars during its first twenty years of use in the United States (128). Other studies estimate that the Federal Government saves ten dollars in medical costs for every one dollar spent on childhood immunization (129). But these economic

128. Bloch AB, Orenstein WA, Stetler HC, et al. Health impact of measles vaccination in the United States. Pediatrics 1985; 76: 524-32.

129. Katz S. Testimony before the Energy and Commerce Subcommittee on

measures should be balanced with more qualitative measures in the full, ethical assessment of vaccination programs.

Despite the benefit derived from and the costs avoided by successful community vaccination programs, vaccine development and administration, like many other areas of scientific and medical endeavor, has been plagued by the increased litigation that characterizes modern American society. In recent liability suits revolving around adverse reactions to vaccinations, the drug companies have been held in strict liability, even though there were determined to be no defects in the manufacturing or administration of the vaccines. In September of 1987, the Federal Court of Appeals for the Western states upheld a $1.3 million damages award for a boy permanently paralyzed after a 1979 administration of DTP. This is only one example that typifies the current legal environment in which vaccination occurs.

According to Julia Ogden of the Association of Trial Lawyers of America Products Liability Medical Malpractice Exchange, vaccine manufacturers have a duty to: 1) develop a drug properly, 2) comply with government regulations, 3) keep up to date on new developments, and 4) warn of side effects. Prior to 1977, the manufacturer only had the duty to warn the prescribing physician of side effects. But after Givens v. Lederle in 1977, this duty to warn by the drug company was extended to patients.

The drug companies who manufacture vaccines have therefore

Health and the Environment, House of Rep.,U.S. Congress, hearings on the effect of cuts in the childhood immunization program. Duke University, Feb. 4, 1982.

claimed that they have been compelled to raise prices in order to regain the losses that they have suffered from legal suits brought against them. Product liability has driven the price of vaccines up dramatically in the last several years. Higher vaccine prices mean reduced cost-effectiveness of vaccination programs.

In 1975, the California Department of Health Services (CDHS) could purchase one dose of DTP for $0.55 to administer in the public sector. By the end of 1986, that price had soared to $11.40, an increase of 1,972%. One dose of OPV cost the CDHS $0.60 in 1975, while the contract cost in 1986 had risen to $8.67, a 1,345% increase. Fig. 5.1 (from the CDHS Disease Control Section, Immunization Unit) illustrates how the component costs of immunization programs in California have drastically changed during a ten-year period.
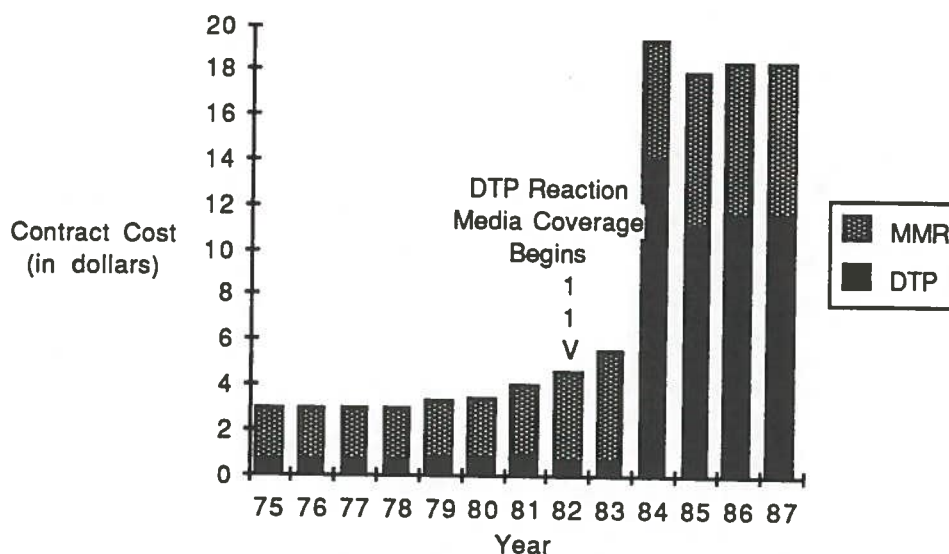
Fig. 5.1. Increases in per vaccine dose contract costs for public vaccine programs, 1975-1987 (data from CDHS).

Due to the complexity of the vaccine market, the increased risk of litigation against vaccine manufacturers not only raises prices but also endangers the availability, distribution, and development of safe

and effective vaccines. Currently, the general availability of vaccines in the United States depends on production by a handful of commercial manufacturers. The main purchaser and distributor of these vaccines, however, is the federal government for use in federally sponsored immunization programs. The federal government also performs or funds most of the lengthy and expensive research necessary for the development of new safe and effective vaccines. The burden of huge damages awards has meant that many drug companies have simply stopped manufacturing and researching new vaccines. For the manufacturers that remain in the marketplace, these trends mean higher prices which are passed on to the consumer. When higher prices are combined with a diminishing number of producers, problems arise not only with the development of new vaccines, but with the availability of established vaccines.

As the result of this myriad of problems, there have been several proposals suggesting various ways in which our society can continue safe and effective vaccination programs without incurring undue expense and while rewarding those individuals who have suffered from their participation in often-mandatory programs that benefit society as a whole. These proposals have almost invariably included two core elements: 1) reducing the legal liability exposure of vaccine manufacturers and administering health care professionals, and 2) providing more effective, equitable, and timely damage awards to vaccine-injured individuals and their families. Since the common tort law system has proven inadequate in addressing these elements, new legislation has been adopted both at the state and federal level.

In November of 1986, President Reagan signed into law the National Childhood Vaccine Injury Act of 1986 which establishes a federal compensation system for people suffering serious adverse reactions to the seven antigens contained in the three vaccines typically required for school or day care entry (DTP, MMR, and OPV). This act acknowledges that there exists necessary but inherently dangerous products for which no-fault remedies are apporopriate. It will require all injury claims to proceed through the compensation system first, but permits parents of injured children to go to court if they reject the compensation award. The law limits the federal compensation to economic losses plus a maximum of $250,000 for pain and suffering and an automatic $250,000 in the event of death. State laws will continue to apply to all civil suits for vaccine injury compensation that seek less than $1,000 awards or in which the petitioner has rejected the award offered by the Federal system. While the enactment of this Federal legislation has great symbolic importance, it has of yet little practical significance since it still awaits Congressional funding.

California has had a similar state law in effect since 1977, in which year the California Immunization Adverse Reaction Fund was established to provide medical care and other services connected with a "severe adverse reaction to any immunization required by state law to be administered to children under 18 years of age." However, in its nine years of existence only five claims have been filed and only two awarded for a total of less than $4,000. The underutilization of the California fund is currently under investigation by the California State Senate Office of Research. North

Carolina has established a much more effective state law, which was enacted in October of 1986 following a $3.5 million jury award in 1985 to a child injured by a DTP dose in 1974.

The impact of these legislative measures can be seen in the leveling-off of price increases in the vaccine market. Since May of 1986, Lederle and Connaught laboratories, leading manufacturers of DTP vaccine, dropped their single-unit price for a 15-dose vial of the vaccine from $170/vial to $133/vial for private physicians in most states. The North Carolina statute, however, leaves the manufacturer free to eliminate the product liability portion of their prices, and DTP can be purchased by North Carolina physicians for only $55/vial. The elimination of the $78.75/vial liability protection surcharge dropped the single dose price of DTP in North Carolina from $8.92 to $3.67 and is predicted to save pediatricians and their patients in that state more than $1 million a year (130).

Summary

The development of regulations surrounding the use of immunizing materials has been outlined from the days of variolation to the present time. Vaccination against the smallpox was made compulsory soon after its advent on many parts of the European continent. England was slower to adopt compulsory measures, but the practice of vaccination in that country fell under increasingly strict control.

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130. American Academy of Pediatrics. N. Carolina gets biggest break as DTP makers cut prices. AAP News 1987; Vol. 3: 1.

Vaccination procedures have fallen under increasingly strict control in the United States as well, but a comprehensive federal code is noticeably absent. The majority of vaccine regulation remains at the state level where it originally developed at a time in American policy history that saw increasing control, regulation, and licensing in a great diversity of areas.

Vaccine production and development occurs today in a complicated legal environment which threatens the availability of cost-effective, life-saving vaccines. Recent local and national legislation has been passed to address the problem of manufacturer liability. While the success of such laws in reducing vaccine cost and increasing availability have been proven at the state level, funding at the national level has not yet been obtained. Congressional appropriation for a national vaccine compensation fund is essential for the continuance of beneficial and cost-effective community vaccination programs.

CONCLUSION

Immunization is an ancient practice which has taken on increasingly important public health and social roles. Variolation had been practiced for many centuries before Jenner's experiments led to the development and spread of vaccination against the smallpox. Since that time, successful vaccines have been manufactured to combat many of the infectious diseases that had previously been responsible for a great deal of human morbidity and mortality. While specific policy implications have been discussed at the conclusion of each section of this paper, it is necessary here to recapitulate the direction in which this field should be headed.

In the United States and other developed countries, immunization levels are high. However, as infectious diseases that were once common become more rare in the population, parents are no longer anxious to place their children in the front of the vaccination line the way they were with the first poliomyelitis immunizations. National vaccination levels in this country are not as high as they should be. Both vaccine requirements and immunization levels are determined at the state level, and compliance with legislation is difficult to obtain. Efforts aimed at accurately assessing and improving immunization levels should be

strengthened, and the monetary backing for such programs must be increased. Like so much of preventive medicine, the public is reluctant to bear the initial cost necessary for successful community vaccination programs, even at the risk of incurring a much greater human and economic cost later.

Unfortunately, just as variolation did, all vaccines carry with them some inherent risk of injury. Technology has made this risk very small, but not unavoidable. Because immunization is in part a social good, educated people are increasingly unwilling to have their children bear the individual risk. In order to avoid the disastrous results of decreasing immunization levels that were witnessed in England and Japan, we need more information with which to make accurate decisions regarding vaccinations. Funds must be allocated to conduct adequate and controlled experiments through which we can assess the true risks associated with individual vaccines. Accurate data regarding the background rates of potential adverse reactions in the absence of vaccination must also be gathered in order to accomplish this goal.

When such studies generate conclusions that cast doubt upon either the safety or efficacy of current vaccines, research must begin immediately for better vaccines. The development of the acellular pertussis vaccine is an excellent example of just such a process. Unfortunately, its widespread use in Japan before controlled studies with large sample sizes had been conducted is also a case of misguided policy. New vaccines must be carefully tested before they are released for public use. More concise federal guidelines outlining

the testing of new vaccines would aid in making this process a smooth one.

Recent vaccine legislation should aid in decreasing the cost of vaccines and increasing their availability in this country. However, when vaccine legislation is passed, careful attention should be paid to its potential for implementation. For instance, as discussed, the new law makes failure by a physician to report a known adverse event following an immunization a crime. This makes a crucial statement about the recognition of under-reporting as a significant problem, but would seem almost impossible to implement. If the event goes unreported, how will it be brought to the attention of the proper authorities?

As a final comment it should be noted that the focus of this paper has been almost entirely culturocentric. Vaccine-preventable infectious diseases are an enormous problem in most of the lesser developed world. Poliomyelitis still cripples many thousands of children a year in parts of Africa. Pertussis, measles, and mumps kill hundreds of thousands more. Many of these countries do not have the technology to deliver or store vaccine preparations that must be kept refrigerated. Vaccines may be unavailable to certain populations because the roads leading to their villages are inaccessible to the vehicles used by health care workers. Also, the cost of purchasing a single dose of vaccine from an American drug company may be more than the annual per capita health expenditure of certain countries.

Drug companies are reluctant to develop vaccines for markets that have no money with which to purchase them. Diarrheal illness

and malaria are two potentially vaccine-preventable illnesses that are the greatest killers in the world. While efforts should and must be made to allocate resources to address the problems discussed in the body of this paper, an effort of incomparable magnitude must be made on a worldwide scale to address the grave burden that infectious diseases still place on humanity.

Appendix One

Calif. State Vaccine Requirements

GUIDE TO IMMUNIZATIONS REQUIRED FOR SCHOOL ENTRY
(Grades K-12)

Post this guide on a wall or desk top as a quick reference to help you determine if pupils seeking admission to your school meet California immunization requirements. If you have any questions, call the Immunization Coordinator at your local health department.

A. IMMUNIZATION REQUIREMENTS To enter or transfer into public and private elementary and secondary schools (grades kindergarten through 12), pupils under age 18 years must have:

	VACCINE	MINIMUM DOSES REQUIRED	ADDITIONAL DOSE REQUIREMENTS FOR SOME PUPILS
I	**Polio - OPV (trivalent oral polio vaccine)[1]**	**3 doses, but. . .**	One more dose if last dose was given before 2nd birthday
II	**Diphtheria, Tetanus and Pertussis**		
	Age 6 years and under (Pertussis is required)		
	DTP or any combination of DTP with DT or Td (tetanus and diphtheria)	**4 doses, but. . .**	One more dose if last dose was given before 2nd birthday
	Age 7 years and older (Pertussis is not required)		
	Td, DT, or DTP or any combination of these	**3 doses, but. . .**	One more dose of Td if last dose was given before 2nd birthday
III	**Measles, Rubella, Mumps[2] Can be given separately or together, e.g. as MMR vaccine.**	**1 dose each, but**	One more dose of any given before the first birthday

[1] If inactivated polio vaccine (IPV) or combination of OPV and IPV was given, at least 4 doses are required. One more dose is required if the last dose was given before the 2nd birthday.

[2] Mumps immunization is not required for pupils 7 years of age and older.

B. EXEMPTIONS See the back of the blue California School Immunization Record (PM286) for instructions about medical or personal beliefs exemptions. An up-to-date list of pupils with exemptions should be maintained separately, so they can be identified quickly if a disease outbreak occurs.

C. PUPILS NOT MEETING REQUIREMENTS Refer pupils who do not meet these State requirements to their physician or local health department, providing them with a written notice giving dates of vaccine doses received and indicating which doses are lacking.

D. DOCUMENTATION - All pupils must present an <u>immunization record.</u>

<u>What is it?</u> - It is a written immunization record, either a personal record with entries made by a physician or clinic, or a school immunization record--the blue California School Immunization Record (PM 286) or another state's school record. It must include at least the month and year <u>each</u> dose was received; for measles, rubella and/or mumps vaccine given in the month of the first birthday, month, <u>day</u> and year are required. A record saying only "up-to-date," "all requirements met," or "series complete" is inadequate. Also, the record must show that all due or past due vaccine doses have been received. Parents cannot simply fill out a California School Immunization Record but must present a written immunization record.

<u>Who must present it?</u> - All pupils entering school or tranferring between school campuses. Kindergarten entrants and entrants from outside the U.S. must present a personal immunization record. Pupils transferring from other schools in California or other states must present either a personal immunization record or a state school immunization record.

<u>When must it be presented?</u> - Kindergarten entrants and entrants from outside the U.S. must present the record at or before entry. Pupils transferring from other schools in California or other states <u>may</u> be given up to 30 school days of attendance while waiting for their records to arrive from the previous school.

<u>What do schools do with it?</u> - School staff must transcribe the immunization dates onto the California School Immunization Record (PM 286), which is available from local health departments. School staff should then review the PM 286 to determine if all immunization requirements have been met. The PM 286 is part of the pupil's permanent cumulative record and must be transferred to the pupil's new school when he/she leaves your school.

E. CONDITIONAL ADMISSIONS Pupils lacking one or more required vaccine doses but <u>not</u> currently due for a dose may be admitted on condition that they receive the remaining doses when due, according to the schedule below. If the maximum time interval has passed, the pupil must be excluded until the next immunization is obtained.

VACCINE	TIME INTERVALS BETWEEN DOSES
Pollo-OPV[a]	2nd dose: 6-10 weeks after 1st dose
	3rd dose: 6-12 months after 2nd dose
DTP (or combination of DTP and DT or Td) - for pupils under age 7 years	2nd dose: 4-8 weeks after 1st dose
	3rd dose: 4-8 weeks after 2nd dose
	4th dose: 6-12 months after 3rd dose
Or	
Td - for pupils age 7 years and older	2nd dose: 4-8 weeks after 1st dose
	3rd dose: 6-12 months after 2nd dose
MMR	None. Only one dose required, which must be received before entry.

a. If IPV (inactivated polio vaccine) is used, follow interval schedule shown for DTP vaccine.

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IMMUNIZATIONS REQUIRED FOR CHILD CARE CENTER ENTRY
Effective September 1986

Post this guide on a wall or desk top as a handy, quick reference for assessing the immunization status of children before they are allowed to attend your center.   If you need more information, please consult the Immunization Coordinator at your local health department.

Important! Parents must present a record of their child's immunizations before he or she can attend your center. It must include the date (at least the month and year) each immunization was received. The immunization history of each child must then be transcribed onto the blue California School Immunization Record (PM 286, available from your county health department) and kept in your files.

Use this table to evaluate each child's immunization status:

Age at Evaluation	Total Vaccine Doses Required By This Age	
Younger than two months.........................	None	
2-3 months...	Polio (OPV)	1 dose
	DTP/DT	1 dose
4-5 months..	Polio (OPV)	2 doses
	DTP/DT	2 doses
6-14 months..	Polio (OPV)	2 doses
	DTP/DT	3 doses
15-17 months...	Polio (OPV)	2 doses
	DTP/DT	3 doses
	Measles, Mumps, Rubella (MMR)	1 dose given on or after first birthday*
18 months through 4 years**.......................	Polio (OPV)	3 doses
	DTP/DT	4 doses
	Measles, Mumps, Rubella (MMR)	1 dose given on or after first birthday*

*MMR is recommended at age 15 months.

**Not legally required but recommended for some children: Haemophilus influenzae type b (Hib) vaccine.

It is the responsibility of the child care center to followup on children under age 18 months to ensure they receive all required immunizations according to the above schedule. Children age 18 months and over who have not met all requirements may be admitted conditionally provided that they have received all currently due immunizations; the center must follow up to make sure the remaining required immunizations are received on time:

Vaccine	Time Intervals
OPV	2nd dose: 6-10 weeks after first dose
	3rd dose : 6-12 months after second dose
DTP/DT	2nd dose: 4-8 weeks after first dose
	3rd dose: 4-8 weeks after second dose
	4th dose: 6-12 months after third dose
MMR	No time interval. Only one dose needed.

Children age 15 months and older should obtain immediately.

STOP DISEASE

Appendix Two

Calif. School Immuniz. Record

CALIFORNIA SCHOOL IMMUNIZATION RECORD

This record is part of the student's permanent record (cumulative folder) as defined in Section 49068 of the Education Code and shall transfer with that record. Local health departments shall have access to this record.

This record must be completed by school and child care center personnel from an immunization record provided by parent or guardian. See reverse side for instructions.

Student Name _____ Sex: M ☐ F ☐ Birthdate _____ Place of Birth _____

Name of Parent or Guardian _____

Telephone (___) _____ Address _____ City _____

VACCINE		DATE EACH DOSE WAS GIVEN				
		1st	2nd	3rd	4th	5th
POLIO (OPV)		/ /	/ /	/ /	/ /	/ /
DTP and/or DT/Td	(Diphtheria, tetanus and pertussis or whooping cough) OR (tetanus and diphtheria only)	/ /	/ /	/ /	/ /	/ /
MEASLES (Rubeola—10 day, red measles)		/ /				
RUBELLA (German measles—3 day measles)		/ /				
MUMPS		/ /				

Some vaccines are available in combination with others such as measles and rubella (M-R) and measles, mumps and rubella (M-M-R). If the student received any combined vaccine, enter the date in each appropriate box.

I. DOCUMENTATION

I certify that I reviewed a record of this student's immunization and transcribed it accurately: Date ___/___/___

Staff Signature _____

Record presented was:
☐ Yellow California Imm. Record
☐ Other immunization record
☐ Out-of-state school record

II. STATUS OF REQUIREMENTS

☐ A. All requirements are met.
Date ___/___/___

☐ B. Currently up-to-date, but more doses are due later. Needs follow-up.

Exemption was granted for:
☐ C. Medical Reasons—Permanent
☐ D. Medical Reasons—Temporary
☐ E. Personal Beliefs

INSTRUCTIONS FOR SCHOOL/CHILD CARE CENTER STAFF

1. Complete student name and address information section, or ask parent or guardian to complete this section only (This form is not to be sent home or given to parents to complete.)

2. School personnel then fill in date (month/day/year) of each immunization the student has received from the Immunization Record presented by the parent or guardian. (If the date consists only of month and year for some doses, fill in month/xx/year; however, if either measles, rubella or mumps (or MMR) was received in the month of the first birthday, month/day/year is required.)

3. Determine if immunization requirements have been met, using the California "Guide to Immunizations Required for School Entry," or "Guide to Immunizations Required for Child Care Center Entry," (available from Immunization Coordinators in local health departments), or other requirements guide.

4. Complete the Documentation and Status of Requirements box.

A. Fill in date and your signature as the school representative who reviewed and transcribed the immunization record presented by the parent or guardian. Check which type of record was presented.

B. If the student has met all immunization requirements, check box A and write in date.

C. If the student has not met all requirements, check box B. Student can be admitted only if up-to-date, e.g. no immunizations due currently. The student must be followed up as indicated in the "Guide to Immunization Requirements."

D. If a student is to be exempted for medical reasons, a doctor's written statement is required; the statement must include which immunization(s) is to be exempted and the specific nature and probable duration of the medical condition. If the medical exemption is permanent, the requirement for the designated immuniza-tion(s) is met; check box A and box C.* If the medical exemption is temporary, check box B and box D, this student must be followed up.*

E. If a student is to be exempted for reasons of personal beliefs, the parent or guardian must sign and date the affidavit below. No other parents should sign this affidavit. All requirements are met; check box A and box E.*

PERSONAL BELIEFS AFFIDAVIT TO BE SIGNED BY PARENT OR GUARDIAN

I hereby request exemption of the child, named on the front, from the immunization requirements for school/child care center entry because these immunizations are contrary to my beliefs. I understand that in case of an outbreak of any one of these diseases, the child may be temporarily excluded from school for his/her protection.

CREENCIAS PERSONALES: DECLARACIÓN JURADA DEBE SER FIRMADA POR EL PADRE O EL GUARDIÁN

Solicito por la presente la exención de mi hijo, nombrado en el reverso, de los requisitos para vacunas de la entrada a la escuela/guardería ya que estas vacunas son opuestas a mis creencias. Comprendo que en caso de un desarrollo en la comunidad de alguna de estas enfermedades, mi hijo puede ser excluido temporalmente de la escuela/guardería por su propia protección.

Signature (Firma) _____

Date (Fecha) _____

* Names of all students in the school/child care center who are exempt should be maintained on an exempt roster for immediate identification in case of disease out-break in the community.

Appendix Three

Serious Adverse Events Following Public Sector DTP Administration in Calif., 1982-84

Manufacturer	Lot Number	Bureau of Biologics Pertussis Mouse Protection Units/1.5ml Individual	Wtd.Avge.	Doses Distributed to local Calif. health depts.	MSAEFI Reports of serious events from public sector with onset < 7 days from vaccine reciept (serious event rate per doses distributed X10E-4)
Wyeth	70901	18.92			
Wyeth	72001	19.53	19.31	107,490	6 (.56)
Wyeth	72101	19.69			
Wyeth	71101	13.13			
Wyeth	71201	13.33	13.21	130,590	4 (.31)
Conn	4A025	13.21			
Wyeth	71401	16.38			
Wyeth	71901	16.80	16.01	80,190	4 (.50)
Wyeth	71501	15.25			
Wyeth	72801	9.84			
Wyeth	73101	8.80	9.11	99,990	5 (.50)
Conn	3346PD	14.19	14.19	162,825	10 (.62)
Conn	3487PL	8.42	8.42	223,860	18 (.80)
Wyeth	71301	23.21			
Wyeth	71801	26.34	26.21	222,420	14 (.63)
Wyeth	72701	27.66			
Conn	4B055	26.41			

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