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New Vaccinations

Lyme Disease, Rotavirus, Hepatitis A and Pneumococcal Disease

Executive Summary

The purpose of this report is to review the use of the new vaccines for lyme disease, hepatitis A, rotavirus, and pneumococcal disease and to inform primary care physicians of the need for vigilant participation in the Centers for Disease Control and Prevention's (CDC) Vaccine Adverse Event Reporting System (VAERS).

This report presents the clinical use of the new vaccines for Lyme disease, rotavirus, hepatitis A and pneumococcal disease. The Lyme disease vaccine is not universally indicated. Instead, its use should be dependent upon individual risk factors, including both geographical and behavioral factors. While the short-term safety of LYMErix has been determined to be adequate, further clinical research on long term sequelae and disease-related events is necessary.[1] Each year in the United States, the rotavirus infection accounts for an estimated 500,000 physician visits, 50,000 hospitalizations and 20-40 deaths.[2] The rotavirus vaccination (RotaShield®), was initially universally indicated by the CDC's Advisory Committee on Immunization Practices (ACIP). On October 22, 1999, the ACIP, after a review of scientific data, no longer recommends vaccination of infants in the United States and withdraws its recommendation that the RotaShield® vaccine be administered at 2, 4, and 6 months of age.[2,3,60] The hepatitis A vaccine is recommended by the ACIP for anyone more than two years of age desiring immunity and anyone in a high-risk group (high-risk groups include travelers, men who have sex with men, illegal drug users, children living in communities with high incidences, and persons with an occupational risk).[4] On February 17, 1999, the ACIP voted to recommend that universal immunization of children be undertaken in states with an incidence of 20/100,000 or higher.[5,6] Minnesota is not one of the eleven states with an incidence of 20/100,000 or greater. The pneumococcal disease vaccine is universally indicated for individuals over 65 years of age, and is recommended for those between the ages of 2 to 64 if they are immunocompromised, have a chronic illness, and/or live in a special environment such as a nursing home. The burden of pneumococcal disease is enormous in the United States, resulting in an estimated 40,000 deaths, 225,000 cases of pneumonia, 52,000 cases of blood infection and 3,000 cases of meningitis per year.[7] This vaccine is of particular importance in the current context of emerging drug-resistant strains of bacteria.

Feed-back from the VAERS system as well as continued emphasis on research into vaccine efficacy and safety are critical components to realizing the complete benefits of vaccination. Although vaccinations have been dubbed this century's greatest public health achievement, they are continually evolving into more safe and effective forms. For this reason, vigilance on the part of primary care physicians is and will remain a critical component of the efficacy and safety of vaccines.

While the benefits of vaccination to society and the individual often outweigh any associated risks, continued clinical surveillance as well as ongoing research and development are essential to the minimization of existing risk.

Recommendations

The Lyme disease vaccine should not be administered universally. It is indicated only for those individuals ages 15-70 living in high-risk geographic areas and engaging in high-risk behaviors.

The rotavirus vaccine has been suspended until further studies can rule out a link to intussusception.

The hepatitis A vaccine should be administered universally in high-incidence geographic locations and to any individual in a high-risk category seeking protection.

The pneumococcal disease vaccine should be administered in certain high-risk groups to minimize illness and the emergence of resistant bacterial strains.

Continued research and development are critical to the identification and minimization of existing risk associated with vaccines.

The participation of primary care physicians in VAERS is needed if it is to be a more effective tool for determining vaccine safety and efficacy.

Introduction

Vaccinations have been dubbed this century's greatest public health achievement, and their routine implementation has resulted in significantly decreased morbidity and mortality in infants worldwide.[8] Although seen by many as a magic bullet, vaccinations are very seldom perfect when initially released by manufacturers, and go through significant growing pains as they evolve. It is critical that physicians, researchers and the public support crucial continued research and development on existing as well as new vaccinations.

History reveals a multitude of common and well-known immunizations that have gone through significant evolution in order to achieve their current levels of efficacy and safety. The first measles vaccines were licensed for use in the U.S. in 1963, and at that time one inactivated and one live attenuated vaccine (Edmonston B strain) were introduced. The inactivated vaccine was not immunogenic and sometimes resulted in infection with atypical measles. The Edmonston B vaccine was withdrawn in 1975 as there was an increased incidence of fever and rash associated with it. Two live, further attenuated vaccines, the Schwarz strain and the Moraten strain, were introduced and subsequently replaced by a fourth vaccine, the currently used Enders-Edmonston vaccine. Each successive strain resulted in fewer adverse events.

In 1969, three vaccines against rubella were licensed for use in the United States: HPV-77:DE-5 (from duck embryo), HPV-77:DK-12 (from dog kidney), and Cendehill strains (from rabbit kidney). HPV-77:DK-12 was withdrawn from the market due to a high rate of associated joint problems. In 1979, all strains were discontinued with the introduction of RA 27/3 (from human diploid fibroblast) which is still currently used. The whole-cell pertussis vaccine was used from its introduction in the 1930's until 1991 unchanged. Concerns about adverse systemic reactions such as convulsions, acute encephalopathy, and lasting brain damage led scientists to develop the acellular pertussis vaccine, which was licensed for use in 1991. Adverse events such as convulsions, persistent crying, and hypotonic hyporesponsive episodes occurred at a higher rate among infants vaccinated with the whole cell vaccine than with the acellular vaccine.

The inactivated poliovirus vaccine (IPV), which is injectable, was first licensed in 1955. With the advent of the live oral poliovirus vaccine (OPV) in 1961, IPV was essentially replaced due to factors such as ease of administration, cost and efficacy. However, with global polio eradication goals almost met and elimination of wild type poliovirus in the Western hemisphere, the risk of paralytic polio associated with OPV is considered unacceptable (the risk is 1 in 52,400,000). In January of 1997, the Advisory Committee on Immunization Practices changed their recommendations for polio to advise that routine childhood immunization consist of two doses of IPV followed by two of OPV.[9] In 1999, the universal childhood immunization schedule was changed by ACIP to reflect these recommendations.[10] On June 17, 1999, the ACIP voted to use IPV for all four doses in childhood immunization.[11] This vote became a final recommendation when it was published in the CDC's October 1, 1999 issue of the Morbidity and Mortality Weekly Report.[56]

The ACIP's recommendation for universal vaccination of infants against hepatitis B has resulted in a closer assessment of thimerosal-containing vaccinations.[10] Concerns over thimerosal, a mercury-containing compound, have recently encouraged the American Academy of Pediatrics (AAP) to release a new set of recommended indications for the hepatitis B vaccine. In July of 1999, the AAP stated that a new thimerosal-free hepatitis B vaccine should be the goal, but until then, vaccination of all infants of mothers who screen negative for HbsAg should be postponed until two to six months of age. Premature infants should not be vaccinated until they are at least 2.5 kilograms and infants of mothers who screen positive for HbsAg should be immunized according to standing ACIP recommendations. In populations where routine screening of pregnant women for hepatitis B antigens is not implemented, all infants should be vaccinated according to current ACIP recommendations.[12,13] With the advent of a thimerosal-free Hepatitis B vaccine in September of 1999, the recommendations reverted to their original form.[57]

On July 15, 1999, the CDC recommended that use of the newly licensed rotavirus vaccine be suspended until at least November of 1999 due to reports of possible increases in intussusception rates in vaccinated infants.[3] This suspension was prompted largely by information gathered by the CDC's vaccine adverse event reporting system (VAERS) and demonstrates how accurate and timely reporting can contribute to the increased safety of vaccinations. On October 16, 1999, the manufacturer of Rotashield withdrew the vaccine from the market until further studies can confirm or deny links between intussusception and the vaccine.[58] The rotavirus vaccine had been recommended for universal use in infants by the ACIP in March of 1999.[2]

Lyme Disease Vaccine

On December 21, 1998, the Food and Drug Administration approved LYMErix$_{TM}$, Smith-Kline Beecham's new vaccine against Lyme disease. The availability of this vaccine has engendered the need for guidelines on its appropriate role in the prevention of Lyme disease. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recently met this challenge when it issued its report "Recommendations for the Use of Lyme Disease Vaccine Recommendations of the Advisory Committee on Immunization Practices". In its statement, the ACIP recommends that decisions regarding vaccine use be based on individual risk factors, both geographic and behavioral.[1] The American Medical Association (AMA) and the American Academy of Pediatrics (AAP) have not released official policy statements regarding the recommended use of this vaccine. This may be due to the fact that universal vaccination is not being advocated and the vaccine is only authorized for use in individuals aged 15 to 70 years. The AMA has, however, endorsed the view that the vaccine should not be used universally, but instead should be targeted to groups of individuals with specific characteristics based on area of residence and participation in high-risk activities.[14] The American Academy of Family Physicians (AAFP) recently released a new policy outlining recommendations for the use of the Lyme disease vaccine which closely resemble the recommendations of the ACIP and the position of AMA.[15] There is general consensus within the medical and public health communities that the use of LYMErix should be targeted to specific groups and this is reflected in all of the referenced literature.

Lyme disease is the most common vector-borne disease in the United States. It is caused by the spirochete (a spiral bacterium of the order Spirochaetales) *Borrelia burgdorferi* and is transmitted by the bite of an infected deer tick *(Ixodes scapularis)* or Western black-legged tick (*Ixodes pacificus)*. The spirochete is not usually transmitted to the host until the tick has been attached for about 36-48 hours and so the successful transmission of the spirochete can be minimized through daily personal examinations for ticks.[16] Symptoms of Lyme Disease may include a bulls-eye shaped rash around the infected bite (erythema migrans), a fever, malaise, stiff neck, headache, fatigue, myalgia, and arthralgia. Manifestations of early-disseminated infection include cardiac, neurologic, and musculoskeletal disease. Late-disseminated disease manifestations include personality changes, sleep disruptions, cognitive disorders (if encephalopathy is present), swelling and pain of joints, and axonal polyneuropathy (pathology of the nervous system, specifically of the axons). If the disease is caught early in its progression (less than three weeks), it is almost always amenable to treatment with antibiotics, most often amoxicillin and doxycycline.[1,17] Personal prevention measures are critical in the control of Lyme disease, such as wearing light-colored clothing with long sleeves and pant legs, tucking pants into socks, checking twice a day for ticks, and using insect repellant with DEET.[1]

Lyme disease is endemic to the Northeast, Upper Midwest (*Ixodes scapularis*) and the West Coast (*Ixodes pacificus*), with these areas together accounting for approximately ninety percent of all reported cases of Lyme Disease in the United States.[14] The CDC has stated that during 1993-1997, a mean of 12,541 cases annually of Lyme disease were reported in the United States, and in 1998, the incidence was 6.06 (per 100,000 people).[1,18] The Minnesota Department of Health documented a total of 261 confirmed cases of Lyme disease in 1998. This translates to an approximate incidence of 5.6/100,000. In Minnesota the cases of Lyme disease are not uniformly distributed throughout the state, so the incidence will vary in different places within the state (Appendix I).[19] In 1998, the state of Connecticut reported an incidence of 90.77/100,000, the highest in the United States. New York, New Jersey, Pennsylvania, Massachusetts, Maryland, Rhode Island, and Wisconsin all had reported 1998 incidences of greater than 10/100,000, or a rate of infection of .0001 or greater.[18]

The Lyme disease vaccine is made from a recombinant *Borrelia burgdorferi* surface lipoprotein with known human immunogenicity, rOspA, as expressed by transformed E. coli cells. This protein is antigenic

and causes a humoral immune response in humans, resulting in the production of anti-OspA antibodies. OspA is expressed primarily by *Borrelia burgdorferi* while it is in the gut of the tick, at initiation of feeding. However, upon passing by the tick salivary gland into the host bloodstream, *Borrelia burgdorferi* predominantly expresses another outer surface lipoprotein, OspC. Therefore, anti-OspA antibody will have its primary effect upon the causative agent in the gut of the tick, as the host blood is ingested, resulting in the destruction of *Borrelia burgdorferi* prior to its entry into the host bloodstream. Therefore, once the *Borrelia burgdorferi* has entered the host and is thus expressing primarily OspC, the LYMErix vaccine is largely ineffective.[1]

Patient Selection

The LYMErix vaccine is not universally indicated. It is for use in individuals aged 15 to 70 years, those living in or traveling to high incidence areas, and those exhibiting high-risk behaviors (hiking, gardening, landscaping). It is not recommended for use in pregnant women, breast-feeding women, immunodeficient individuals, persons with musculoskeletal disease or with treatment-resistant Lyme arthritis.[20] The vaccine is administered in three doses at zero, one and twelve months, with protective boosters potentially needed on an undetermined basis.

Effectiveness

The major efficacy trial conducted by The Lyme Disease Vaccine Study Group enrolled 10, 936 people at 31 sites in 10 different states with very high incidences of Lyme disease. Of these, 5469 were administered vaccine, while 5467 were administered placebo. The vaccine consisted of 30 µg of lipidized rOspA adsorbed to an aluminum hydroxide adjuvant in phosphate-buffered saline. The placebo was identical except did not contain the lipidized rOspA. The vaccine was determined to be 49% effective after the first two dosages, and 76% effective after all three in definite cases of Lyme disease.[21] In asymptomatic Lyme disease, as determined by Western blot seroconversions, the efficacy jumps to 83% after the first two dosages, and up to 100% after the full course of injections.[1] The LYMErix vaccine is associated with local reactions including soreness (24.1%), swelling and redness (less than 2%), and systemic reactions including fever, chills, and myalgia (less than 3.2%). The occurrence of late events or clinical syndromes in the vaccine group was not statistically significantly higher than in the placebo group.[21]

While the short term safety of LYMErix was determined to be adequate in the efficacy trial, further research on long term chronic sequelae and disease-related events is necessary. One particular concern over the long term safety of the Lyme disease vaccine is the possibility that it may trigger arthritis or paresthesias in genetically prone individuals. Individuals who exhibit the HLA type DR4 genotype (the human leukocyte antigen type DR4) are predisposed to rheumatoid arthritis, which is considered to be an autoimmune disease. Individuals with this genotype are also predisposed to treatment-resistant Lyme arthritis, possibly because the protein hLFA-1 (human leukocyte function associated antigen), which has a high binding affinity to HLA-DR4, has a high homology with OspA. This may result in the anti-rOspA antibodies acting as autoantibodies against the hLFA-1 protein when it is presented by HLA-DR4.[14,22] There are general concerns that this vaccine may result in a "late unanticipated event" and that vaccinees should be followed carefully for at least 5-10 years after vaccination to obtain appropriate data on long term effects.[23] The issue of booster shots after initial vaccination to maintain anti-OSA antibody titers needs to be researched. Since children under the age of fifteen comprise a large portion of those individuals at-risk, the vaccine needs to be modified so it is indicated for children under fifteen. Finally, this vaccination will result in routine false-positives when testing is done with the traditional ELISA method, and the CDC suggests using Western blotting instead when testing a vaccinated individual for Lyme disease.[1]

Cost

Universal administration of LYMErix is not cost-effective at currently reported statewide incidences. Meltzer et al. report that with a total vaccine cost of $200, vaccine efficacy of .85, probability of early diagnosis and treatment of .80, and probability of Lyme disease infection of .005 (500/100,000), the cost per case of Lyme disease averted is $39,761.[24] Currently, a single vaccine dose costs $49, which in addition to administration costs, amounts to a total vaccine cost of approximately $200 for the three shot series. The highest reported incidence of Lyme disease in 1998 was in Connecticut, at 90/100,000, or .0009. The vaccine efficacy, according to the literature, ranges from 78% in cases of symptomatic Lyme disease to 100% in cases of asymptomatic Lyme disease (.78 - 1.0). The estimate of .80 for the

early diagnosis of Lyme disease may result in the understatement of disease related costs, as the range suggested in the literature for early diagnosis varies from .60 - .90. A recent report by the Institute of Medicine describes a system for ranking the relative cost-effectiveness of pursuing either research and development of candidate vaccines or of implementing vaccine programs.[25] This report ranks those vaccines costing in excess of $100,000/QALY (quality-adjusted life year) saved as less favorable. The universal administration of the Lyme disease vaccine falls into this category.

Rotavirus Vaccine

The tetravalent, oral, live rotavirus vaccine, RotaShield® (Wyeth-Ayherst), was approved for use in infants by the FDA on August 31, 1998. Rotavirus is a 70-nanometer-diameter icosahedral virus composed of three capsid protein layers and 11 double-stranded RNA segments.[31] It contains three major antigenic proteins, one of which, viral protein 7 (VP7) a G-type surface protein, is specifically used in the tetravalent RotaShield vaccine. Using gene reassortment, the VP7 gene from three of the four human serotypes was incorporated into the rhesus rotavirus, making three single-gene human-rhesus reassortants. The VP7 gene present in the native rhesus rotavirus strain provides immunity to the fourth human serotype.[27] Using a combination of the native rhesus rotavirus and the three reassortant strains, the tetravalent RotaShield will protect against all four significant human rotavirus serotypes.

On July 15, 1999, the CDC recommended that use of the newly licensed rotavirus vaccine be suspended until at least November of 1999, due to reports of possible increases in intussusception rates in vaccinated infants.[3] Prior to that, the rotavirus vaccine had been recommended for universal use in infants by the ACIP in March of 1999.[2] However, on October 22, 1999, the ACIP, after a review of scientific data which indicated a strong association between RotaShield and intussusception among some infants during the first 1-2 weeks following vaccination, withdrew its recommendation of the RotaShield® vaccine.

Patient Selection

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) originally released its recommendation for universal vaccination of infants on March 19, 1999. The vaccination was recommended to be administered at 2, 4 and 6 months of age, but not after 7 months of age due to declines in maternal antibodies and subsequent increases in febrile illness associated with the vaccination. The entire three-dose course was to be completed within the first year of life, as data regarding both efficacy and safety in children aged one or older was not adequate. If the vaccination series was initiated late, then each dose was to be at least three weeks apart.[2] Prior to their withdrawal of the vaccine, the ACIP revised its recommendations to encourage immunization of premature infants if they met the following three requirements: greater than six weeks of age, leaving the nursery or no longer hospitalized, and clinically stable. At that time, the ACIP suggested that although there may be more risks for premature infants from the vaccine, the rotavirus infection itself also poses a large threat, and so costs and benefits of both options must be weighed properly.[26] The vaccine was recommended for breast-fed infants and those who have had rotavirus gastroenteritis previously, and for those who had a mild illness with no fever. RotaShield could be safely administered simultaneously with DTP (or DTaP), Hib vaccine, OPV, IPV, and hepatitis B.[27] RotaShield was not be given to immunocompromised infants, infants with acute to moderate gastrointestinal disease, moderate to severe febrile illness, preexisting chronic gastrointestinal disease or infants allergic to any part of the vaccine. If an infant regurgitated a dose of the vaccine, it was not be re-administered, as data on the safety of higher doses was not sufficient. The American Academy of Pediatrics (AAP) had also released a recommendation for universal rotavirus vaccination at ages 2, 4 and 6 months. The recommendations of the ACIP and the AAP were very similar, except the AAP suggested not to initiate the course of vaccinations after six months of age, while the ACIP suggested seven months of age.[28] The American Academy of Family Physicians (AAFP), however, did not support universal vaccination, and released a set of recommendations which stated that rotavirus vaccination should be an individual decision made collaboratively by the parents and physician.[29] The rotavirus vaccination was added to the Recommended Childhood Immunization Schedule for 1999 prior to the recall of the rotavirus vaccine.[30]

Effectiveness

The rotavirus vaccine was determined to be both safe and acceptably effective in several clinical trials. However, based on the results of an expedited review of scientific data presented to the ACIP by CDC in cooperation with the FDA, NIH, and Public Health officials, along with Wyeth-Lederle indicated a strong

association between RotaShield and intussusception leading to its withdrawal on October 22, 1999.[60] Originally, it was thought that the adverse events found to be associated with vaccine administration to more than 10,000 children included a mild fever in up to 15% of recipients, a moderate fever in about 1% of recipients, loss of appetite, fussiness and fatigue.[32] The febrile response usually occurred on the third or fourth day following vaccine administration. There was thought to be no statistically significant difference in occurrence of diarrhea, intussusception, vomiting, coughing or rhinitis in placebo-controlled clinical safety trials. However, one efficacy study in Finland found a higher rate of diarrhea in vaccinated children than in placebo recipients.[2,33] Four efficacy trials for RotaShield in the United States and Finland determined that the vaccine demonstrates 49%-68% efficacy against any rotavirus infection, 69%-91% against severe diarrhea, and 50%-100% efficacy in prevention of visits to the physician's office.[2] In one trial in Finland, the efficacy of the vaccine in preventing hospitalizations was examined, and the protection was determined to be 100%.[33] As was expected by vaccine-developers, RotaShield protected most effectively against severe disease, enhancing its overall cost-effectiveness.

Cost

Rotavirus is the most common cause of severe childhood gastroenteritis and exhibits symptoms including diarrhea, fever, abdominal cramping, and vomiting and often results in severe dehydration. Four out of five children are infected before the age of five, resulting in approximately 3.5 million infected children in the United States per year. This results in 500,000 physician visits, 50,000 hospitalizations and 20-40 deaths a year in the U.S.[2] Worldwide, as many as 870,000 children die from rotavirus infection per year.[34] A study by Tucker et al. demonstrates the cost-effectiveness of the RotaShield vaccine when administered routinely and universally to infants. Direct medical costs are estimated at $264 million, and societal costs at $1 billion, which upon threshold analysis yields a break-even cost of vaccine of $9 a dose for the health care system and $51 a dose for society.[35] With current prices ranging from $20 a dose to $38 a dose, universal vaccination against rotavirus is always cost-effective for society.[32,36] The cost of vaccine, vaccine efficacy, and disease burden all affect the cost-effectiveness of a universal vaccination program. According to a forthcoming report by the Institute of Medicine, the rotavirus vaccine falls into the favorable category, as it incurs a cost of between $10,000 and $100,000 per QALY (quality-adjusted life year) saved.[25]

The development of a vaccine against rotavirus is extremely important considering that there is apparently no reliable prevention method for controlling its spread. The rates of infection are the same among children in developing and developed countries, so hygiene measures and clean water have had little effect on the rates of transmission of rotavirus.[2] In a clinical efficacy study in Caracas, Venezuela, it was found that members in both the placebo group and vaccine group shed a vaccine virus, indicating that there is transmission of this virus in the community.[37] This indicates that vaccinated individuals may confer resistance to rotavirus to non-vaccinated individuals.

Hepatitis A Vaccine

Two hepatitis A vaccines, HAVRIX® (SmithKline Beecham) and VAQTA® (Merck), are available for use in the United States. Hepatitis A, caused by a 27-nm non-enveloped RNA picornavirus (enterovirus) with only one serotype, is native to humans but can be harbored in primates. Both HAVRIX and VAQTA are composed of whole, formalin-inactivated hepatitis A virus particles adsorbed onto aluminum hydroxide, administered in a two-shot series given at least six months apart. While HAVRIX is currently licensed in three formulations with varying E.L.U.'s (ELISA units), VAQTA is licensed in two formulations, with varying U's (units of antigen). Neither is indicated for children less than two years of age, individuals with moderate to severe illness, individuals who are allergic to any component of the vaccine, and, as only limited data for pregnant women is available, pregnant women.

Patient Selection

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) published a set of recommendations for use of the hepatitis A vaccine, which state that it should be used for anyone over the age of two who desires immunity, and persons in a high-risk group. High risk groups include travelers, children living in communities with high rates of infection, men who have sex with men, illegal drug users, persons with an occupational risk for infection (research laboratory setting or those working with primates), persons with chronic liver disease, and persons with clotting-

factor disorders.[4] Safety, immunogenicity and efficacy studies are currently underway for Avaxim, a new childhood vaccine for hepatitis A which could be used in children as young as 18 months.[38] The recommended use guidelines published by The American Academy of Pediatrics (AAP) are very similar to those of the ACIP, also suggesting that vaccine use be restricted to individuals older than two years of age and in high-risk groups.[39] Both guidelines recommend passive immunization with gamma globulin for postexposure prophylaxis, as there is limited data available regarding the efficacy of the vaccine in this situation. Both the American Medical Association (AMA) and the AAP concur with these recommendations, noting that the highest rates of infection are usually found in children aged 5 to 14 years of age, and therefore that immunization of children and adolescents is particularly germane when considering incidence reduction.[40,41]

On February 17, 1999, the ACIP voted to recommend that universal immunization of children be undertaken in states with an incidence of 20/100,000 (.0002) or higher.[6] This includes eleven states: Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Nevada, California, and Idaho. Oklahoma has instituted state school entrance requirements that include hepatitis A immunization for children entering kindergarten and seventh grade.[42,43] In Maricopa county in Arizona, vaccination is required for children ages 2 to 5 for day care entry, and both Texas (select counties) and Alaska are implementing routine vaccination programs, although there are no concurrent school entry requirements.[44] For states with an incidence ranging between 10/100,000 and 20/100,000, routine immunization should be considered, according to the ACIP. The current average national incidence in the U.S. is 10/100,000. Other states are expected to institute routine hepatitis A vaccination for children in response to the new ACIP recommendations, although funding is a consideration.[42]

Effectiveness

The efficacy of the HAVRIX vaccine, evaluated in a double-blind placebo-controlled randomized study on 40,000 children ages 1 to 16 in Thailand, was determined to be 94%. For VAQTA, the efficacy rate was found to be 100% as determined by a study of 1000 children in New York. Although hepatitis A does not result in chronic disease, it is a cause of serious morbidity and even in some cases, mortality. In the United States, it is estimated that 150,000 cases of hepatitis occur per year, with fulminant hepatitis resulting in approximately 100 deaths per year for a case-fatality rate of approximately 0.3%. Symptoms include dark urine, nausea, vomiting, diarrhea, jaundice, appetite loss and fatigue and there is little treatment for the disease besides rest and proper diet. The route of transmission is oral-fecal, with the majority of transmission occurring in private homes but occasionally occurring via contaminated food or water. The incubation period averages 28 days, with symptoms lasting up to two months. Children under six years of age are usually asymptomatic, and therefore constitute a primary source of transmission.[4] HAVRIX and VAQTA have been administered to over 59,000 people in clinical trials and are associated with mild problems, such as soreness at injection site, headache, loss of appetite, and fatigue. Occurrence of serious adverse reactions in the vaccinated group were not documented at levels above expected background incidence.

Cost

With approximately 150,000 cases of hepatitis A per year in the United States, costs range up to as much as $450 million dollars per year (medical and social costs). A study by Dr. Ananya Das indicates that the strategy of universal vaccination, with outcome measures of cost per person and quality life years gained, is cost-effective, with a marginal cost-effectiveness ratio of $12, 833.[45] According to a report by the Institute of Medicine, with a cost of $12,833 per QALY (quality-adjusted life year) saved, universal vaccination against hepatitis A falls into Level III, the favorable category. The study also determined that a strategy of screening for antibody followed by vaccination when appropriate was cost-effective, with a cost-effectiveness ratio of $7,267.[45] According to the Institute of Medicine study, this strategy would fall into Level II, the more favorable category, with a cost of $7,267 per QALY.[25] Das' study also found that when the cost of the two-dose vaccination fell below $57, the strategy of universal vaccination was favored over the screen and vaccinate strategy. With current costs of about $33 per dose, the screen and vaccinate strategy may be more cost-effective than universal vaccination.[46] A new study on a combined pediatric hepatitis A/ hepatitis B vaccine indicates that it is both safe and efficacious in children ages 1 to 16.[47] This finding will most likely result in significantly reduced associated costs of administration, making implementation of universal vaccination more attractive. The hepatitis B vaccination is already universally indicated and is listed on the recommended child immunization schedule released by the ACIP.

Pneumococcal Disease Vaccine

The two vaccines currently available for pneumococcal disease, Pneumovax 23® (Merck) and Pnu-Immune 23® (Lederle Laboratories) have been available in their present form since 1983, when their licensure allowed for the replacement of an existing 14-valent vaccine. Pneumovax and Pnu-Immune are made of purified capsular polysaccharide antigen from 23 serotypes known to cause invasive disease (isolated from the blood of infected individuals). These 23 serotypes account for 85-90% of all invasive pneumococcal disease. A single dose contains 25 mg of each capsular polysaccharide antigen dissolved in saline solution with either phenol or thimerosal as a preservative.

Patient Selection

With an alarming increase in the incidence of bacterial resistance to antibiotics, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends extensive use of the vaccine in certain populations in an attempt to deter the emergence of multi-drug resistant strains of Streptococcus pneumoniae bacteria. ACIP recommends that individuals in the following groups receive a pneumococcal disease vaccination: those aged greater than or equal to 65 years of age, those aged 2 to 64 years with a chronic illness or functional or anatomic asplenia, those living in a special environment (nursing home, long-term care facility), and immunocompromised individuals.[7] Revaccination is particularly important, and is suggested for those with unknown immunization status, those older than 65 if more than five years have elapsed since immunization, those sensitive to infection and older than 10 years if more than five years have elapsed, and those sensitive to infection and younger than 10 years if more than three years have elapsed.[48] In March of 1999, the American Medical Association (AMA), in conjunction with ten other professional medical organizations, released a Quality Care Alert stating the critical importance of immunization against Streptococcus pneumoniae in high-risk groups and revaccination efforts.[49] The American Academy of Pediatrics (AAP) states that there are over 340,000 individuals aged 2 to 18 years who have chronic diseases, placing them in the high-risk group for invasive pneumococcal disease. AAP recommends that these individuals receive vaccination, and that those at the highest risk for rapidly decreasing antibody titers (immunocompromised individuals) receive revaccination every three or five years, depending on the age of recipient.[40] Adult immunization is often very difficult to achieve, and it is currently estimated that less than 45% of those over 65 years of age are immunized. This is of particular concern in the context of emerging drug-resistant strains of bacteria.

Effectiveness

The vaccines for pneumococcal disease generally demonstrate high rates of efficacy against invasive disease, ranging from 56%-81% as demonstrated in controlled clinical trials in South Africa, France, and case-controlled studies.[50] The rate among those aged 65 years or greater was 75%, while the rate within specific groups (those with anatomic asplenia, diabetes mellitus, chronic pulmonary disease, congestive heart failure, and coronary heart disease) ranged from 65%-84%. Vaccine efficacy has not been established in immunocompromised individuals and it is thought that these individuals will have a poor antibody response to the antigens in the vaccine (due to age or immunosuppressive treatment). The vaccines are effective only against invasive disease (bacteremia and meningitis) and pneumococcal pneumonia and are not proven to be effective against sinusitis or otitis media. Furthermore, the vaccines are not immunogenic in children aged less than two years. In children of this age the immune system is immature, and the induced antibody response, which is T-cell-independent, is often inconsistent and not adequate enough to provide protection when challenged with Streptococcus pneumoniae. The vaccine is safe, and has been used since 1977. The most common adverse reactions are pain, redness and swelling at the site and erythema. Other reactions, such as anaphylactic, systemic or severe local reactions, are extremely rare. The vaccine is not indicated for those less than two years of age, those with an allergy to any of the vaccine components and pregnant or nursing women.[7] The symptoms of pneumococcal disease include shaking chills, cough, fever, chest congestion, headache and greenish, rusty or yellowish sputum.[51] Treatment is currently not reliable due to increasing bacterial resistance to antibiotics, and therefore vaccination, especially in vulnerable individuals, is critical.

Cost

The burden of pneumococcal disease is enormous in the United States, as well as worldwide. It accounts for approximately 40,000 deaths, 225,000 cases of pneumonia, 52,000 cases of blood infection, and 3,000 cases of meningitis per year in the United States. The incidence of pneumococcal bacteremia is 15-

30/100,000 and the incidence of pneumococcal meningitis is 1-2/100,000.[7] Worldwide, more than 1.2 million children die from pneumococcal disease.[52] In a cost-effectiveness study conducted by Sisk et al. the pneumococcal vaccine was found to be both cost-effective and cost saving. It concluded that if 23 million unvaccinated individuals over the age of 65 had been vaccinated, 78,000 years of healthy life would have been gained, and $194 million would have been saved. The vaccination was considered cost saving in those older than 65 years if the vaccine cost $20 or less, and in the year 1993, Medicare covered the vaccine at $12.[53] With the base case analysis revealing cost savings per quality-adjusted life year (QALY), the Institute of Medicine ranked the vaccine for pneumococcal disease, in the Most Favorable category, as it saves both money and QALY's. The Institute of Medicine suggests that this ranking is dependent upon vaccination of populations greater than 65 and less than two.[25] There is currently a vaccine, PNCRM7, being developed by Wyeth-Lederle which has proven to be safe in clinical trials, and which was shown to be 100% effective in clinical studies. As a result of these promising results, the vaccine has been given fast-track development status by the FDA. The vaccine is a seven-valent vaccine which will protect against invasive pneumococcal disease and otitis media, which cause up to 30 million pediatric visits a year in the United States.[54] The study by Sisk et al. provides strong economic and health reasons for the extensive use of the vaccines for pneumococcal disease.

VAERS

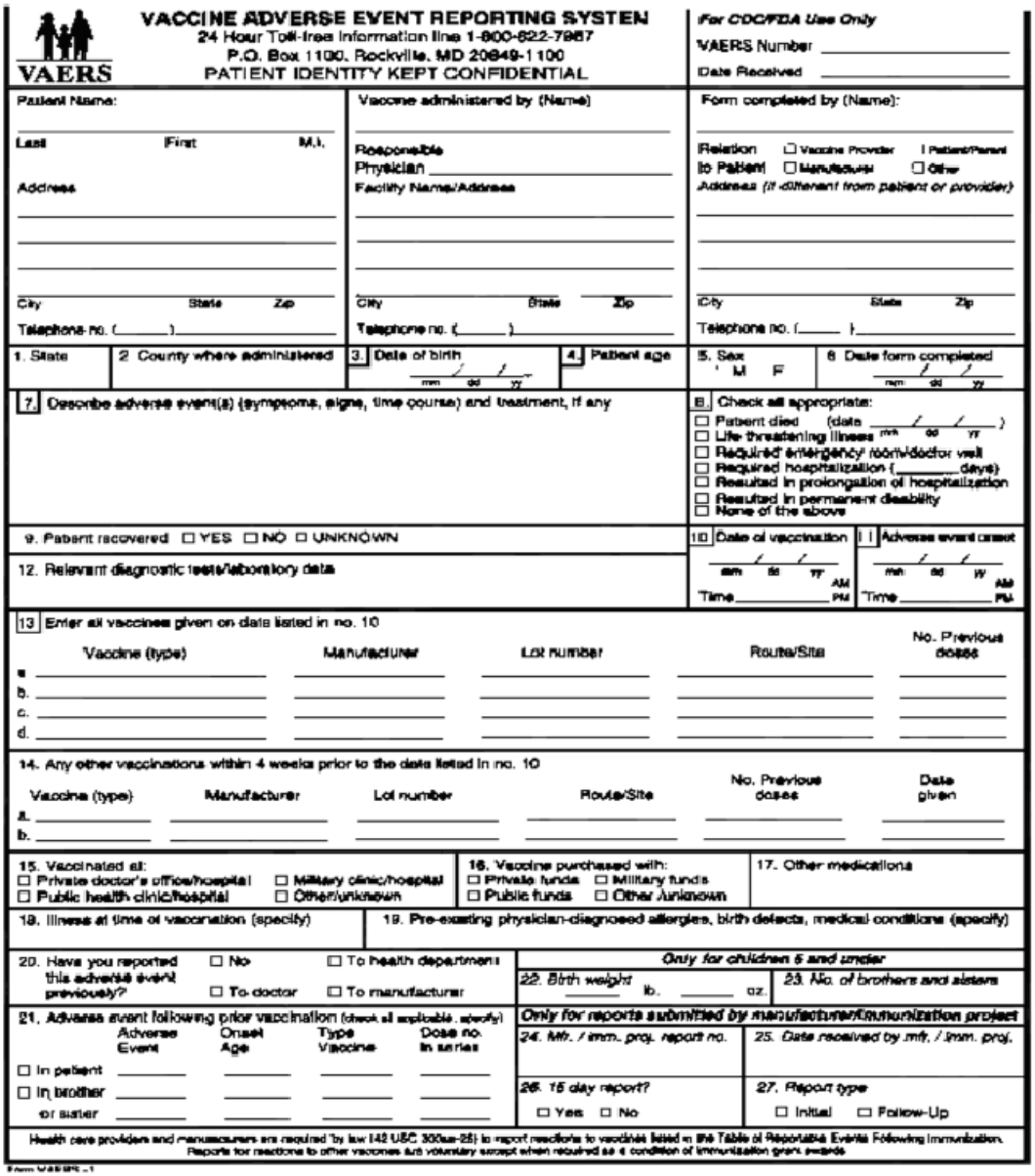
Immunizations represent the intersection of personal health care and public health initiatives. It is critical that research and development efforts continue to be supported by the medical, scientific and public health communities as vaccines are continually evolving as we gain more knowledge about disease processes and immunology. This continuing evolution prompted the CDC to establish the Vaccine Adverse Event Reporting System (VAERS) in November 1990 for use in the ongoing evaluation of the safety and efficacy of vaccines. VAERS is a particularly important tool for determining vaccine safety and its use should be promoted by physicians and manufacturers. VAERS accepts reports of any adverse event following vaccination and compiles the information, allowing the CDC to track any unusual epidemiological trends associated with vaccine safety. Appendix I contains a copy of the VAERS reporting form. For information on how to contact the VAERS program see Appendix II.

Although the data is subject to limitations, VAERS cannot be a totally successful tool without physician reporting. Each report provides information that is compiled to assess vaccine safety. Complete and accurate reporting of post-vaccination events supplies public health professionals with the information they need to ensure the safest strategies of vaccine administration. From January 1991 to December 1996, only 14.5% of the reports received by VAERS were from private health care providers, while 71.8% were from manufacturers and public health departments.[55] Physicians must be willing to foster the VAERS system by making parents aware of the possibility of a post vaccine adverse event and encouraging reporting of such events. VAERS is a tool that allows the scientific and medical community to further reduce risks associated with vaccines. Without personal alertness and advocacy at the individual level on the part of private health care providers, VAERS can not reach it's envisioned potential.

Recommendations

- The Lyme Disease vaccine should not be administered universally. It is indicated only for those individuals ages 15-70 living in high-risk geographic areas and engaging in high-risk behaviors.
- The Rotavirus vaccine has been suspended until further studies can rule out a link to intussusception.
- The Hepatitis A vaccine should be administered universally in high- incidence geographic locations and to any individual in a high-risk category seeking protection.
- The pneumococcal disease vaccine should be administered in certain high-risk groups to minimize illness and the emergence of resistant bacterial strains.
- Continued research and development are critical to the identification and inimization of existing risk associated with vaccines
- The participation of primary care physicians in VAERS is needed if it is to be a more effective tool for determining vaccine safety and efficacy.

Appendix I: The VAERS Reporting Form[55]



VACCINE ADVERSE EVENT REPORTING SYSTEN
24 Hour Toll-free Information line 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number
Date Received

Patient Name: Last First M.I.
Address
City State Zip
Telephone no. ( )

Vaccine administered by (Name)
Responsible Physician
Facility Name/Address
City State Zip
Telephone no. ( )

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address (if different from patient or provider)
City State Zip
Telephone no. ( )

1. State | 2. County where administered | 3. Date of birth mm dd yy | 4. Patient age | 5. Sex M F | 6. Date form completed mm dd yy

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm dd yy)
☐ Life-threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____ days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm dd yy Time AM PM

11. Adverse event onset mm dd yy Time AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously?
☐ No ☐ To health department
☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight lb. oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr. / imm. proj. report no.
25. Date received by mfr. / imm. proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS -1

DIRECTIONS FOR COMPLETING FORM

Additional pages may be attached if more space is needed.

GENERAL

Use a separate form for each patient. Complete the form to the best of your abilities. Items 3, 4, 7, 8, 10, 11, and 13 are considered essential and should be completed whenever possible. Parents/Guardians may need to consult the facility where the vaccine was administered for some of the information (such as manufacturer, lot number or laboratory data.)

Refer to the Reportable Events Table (RET) for events mandated for reporting by law. Reporting for other serious events felt to be related but not on the RET is encouraged.

Health care providers other than the vaccine administrator (VA) treating a patient for a suspected adverse event should notify the

VA and provide the Information about the adverse event to allow the VA to complete the form to meet the VA's legal responsibility. These data will be used to increase understanding of adverse events

following vaccination and will become part of CDC Privacy

Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems". Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

Postage will be paid by addressee. Forms may be photocopied (must be front & back on same sheet).

SPECIFIC INSTRUCTIONS

Form Completed By: To be used by parents/guardians, vaccine manufacturers/distributors, vaccine administrators, and/or the person completing the form on behalf of the patient or the health professional who administered the vaccine.

Item 7: Describe the suspected adverse event. Such things as temperature, local and general signs and symptoms, time course, duration of symptoms diagnosis, treatment and recovery should be noted.

Item 9: Check "YES' if the patients health condition is the same as it was prior to the vaccine, 'NO' if the patient has not returned to the pre-vaccination state of health, or UNKNOWN" if the patient's condition is not known.

Item 10: Give dates and times as specifically as you can remember. If you do not know the exact time, please

Item 11: indicate "AM" or "PM" when possible if this information is known. If more than one adverse event, give the onset date and time for the most serious event.

Item 12: Include "negative" or "normal" results of any relevant tests performed as well as abnormal findings.

Item 13: List ONLY those vaccines given on the day listed in Item 10.

Item 14: List any other vaccines that the patient received within 4 weeks prior to the date listed in

Item 16: This section refers to how the person who gave the vaccine purchased It, not to the patient's insurance.

Item 17: List any prescription or non-prescription medications the patient was taking when the vaccine(s) was given.

Item 18: List any short term Illnesses the patient had on the date the vaccine(s) was given (i.e., cold, flu, ear Infection).

Item 19: List any pre-existing physician-diagnosed allergies, birth defects, medical conditions (including developmental and/or neurologic disorders) for the patient.

Item 21: List any suspected adverse events the patient, or the patient's brothers or sisters, may have had to previous vaccinations. If more than one brother or sister, or if the patient has reacted to more than one prior vaccine, use additional pages to explain completely. For the onset age of a patient, provide the age in months if less than two years old.

Item 26: This space Is for manufacturers' use only.

Appendix II: VAERS Contact Information[55]

Who can report to VAERS?

Any one can report to VAERS. VAERS reports are usually submitted by health care providers, vaccine manufacturers, and vaccine recipients (or their parents/guardians). Patients, parents, and guardians are encouraged to seek the help of a health care professional in reporting to VAERS.

The Reportable Events Table specifically outlines the post-vaccination events which must be reported. The need to report is also based on the amount of time which elapsed between the vaccination and the start of the event. A copy of the table can be obtained by calling VAERS at 1-800-822-7967.

How do I report to VAERS?

A VAERS report form, pre-addressed to VAERS and postage-paid, is used to report pertinent information, including a narrative description of the adverse event.

For a VAERS report form for assistance in filling them out call VAERS at 1-800-822-7967 or visit the VAERS web site at.

How can I find additional information?

To find additional information on the VAERS program and vaccine information, visit the FDA website at.

VAERS does not provide specific vaccine information, the Center for Disease Control (CDC) has a vaccine hotline to answer questions related to vaccines and immunizations. The CDC Vaccine Hotline is 1-800-232-2522.

Appendix III: Public Comment

Public Comment from Dr. Alan Lifson, MDH on the Vaccination Report:

1. Concerns about the use of the phrase "growing pains" in the first paragraph of the Introduction, page 2. Want to assure the public that the vaccines are thoroughly tested before release.
2. Two updates on information regarding the ACIP on page 3: the first is that the ACIP's recommendation to make Hepatitis A vaccination universal for all states with an incidence of 20/100,000 or greater was finalized. Second, a thimerosal-free Hepatitis B vaccine has been formulated and is recommended for use by the ACIP.
3. Comments that the key issue to the high MN incidence for Lyme Disease is its distribution (page 5).
4. Bottom of page 5: concerns that it appears as if previous uncomplicated Lyme disease is a risk factor on its own. In fact, it is more this in combination with geographical and behavioral risk factors.
5. Page 6, comments that a big problem with Lyme Disease vaccine is that it is not recommended for children under 15, and that this group is actually generally at very high risk for contracting the disease.
6. Generally concerned about the entire Rotavirus vaccine section and its applicability in light of its recent withdrawal by the CDC as well as the withdrawal by the manufacturer.
7. Page 12: worth highlighting further the fact that children are big source of Hepatitis A transmission because they are usually asymptomatic.
8. Comment on page 12 that the Favorable Category for the Hepatitis A vaccine (the IOM rating) would maybe be dependent upon the rate of infection in the immunized population.
9. Concerns about the accuracy of the recommendations for revaccination with pneumococcal vaccine on page 13.
10. Comments generally that there is controversy over whether the pneumococcal vaccine is effective against pneumococcal pneumonia.
11. Mentions limitations of VAERS- for example, just because an adverse event comes after the administration of a vaccine, the vaccine isn't necessarily implicated. Public Comment from Dr. Alan Lifson, MDH on the Vaccination Report.

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