Alternative vaccination schedules (AVS): detection of AVS in New York State using immunization registry data

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Abstract

Intentional deviation from the recommended childhood vaccine schedule (RVS), referred to as an alternative vaccination schedule (AVS) is becoming increasingly prevalent in the United States. Physicians may accommodate vaccine-hesitant parents with an AVS as a compromise position to allow some vaccinations to be given, but in doing so children remain vulnerable to vaccine-preventable disease for a longer period of time. This research expands upon the nascent literature by proposing a unified definition of AVS, quantifying the prevalence of infants following an AVS in New York State (NYS) (exclusive of New York City) by geographic area and community and medical practice characteristics.

The prevalence of AVS was determined by reviewing records in the NYS Immunization Information System (NYSIIS). Descriptive statistics compared children following the RVS or an AVS based on number of visits, age at visit, and age appropriate up-to-date status. Community characteristics were determined by linking vaccine records to census data by zip code. Medical practice characteristics came from NYSIIS.

The proportion of infants following an AVS in NYS between 2009 and 2011 was 24%. Only 13% of infants following an AVS were up-to-date by nine months of age compared to 90% of infants following the RVS (p < .0001). Among up-to-date infants, AVS infants take, on average, seven extra weeks to become up-to-date compared to RVS infants (25 vs. 18 weeks, p < .0001). Vaccination following an AVS was positively correlated with both median household income (r=0.46, p<.0001) and education (r=0.38, p<.0001). The median proportions of children following an AVS were highest in urban practices (25%) and practices caring for fewer than 100 children (33%).
One in five infants are following an AVS in NYS and are significantly less likely to be up-to-date at nine months of age compared to infants following the RVS. These children generally live in communities with higher socio-economic status and frequent smaller clinical practices. This research suggests where to focus both parental and provider education to improve childhood vaccination rates.
Chapter 1. Background

1.1 Vaccination in the United States

1.1.1 History of Vaccine Development

Vaccination in the modern era is generally considered to have begun with the development of the smallpox vaccine in 1789 by Edward Jenner. A hiatus of almost 100 years passed, however, before Louis Pasteur created the first rabies vaccine in 1885. During the 19th century, vaccine discovery and development accelerated, and by the end of the century vaccines had also been created to protect against cholera, typhoid, and plague. During the 20th century vaccines were created and refined to protect against a myriad of diseases including: yellow fever, diphtheria, pertussis, tetanus, polio, measles, mumps, rubella, meningococcal disease, pneumococcal disease, Haemophilus influenzae type b, hepatitis B, hepatitis A, influenza, and varicella, among others. More recently, vaccines against rotavirus and human papilloma virus have also been developed.

Today, scientists strive to create vaccines that are safer, more effective, provide broader coverage against various strains, and offer combination protection against several diseases in one product. The Centers for Disease Control and Prevention (CDC) estimate that the use of these vaccines has reduced the incidence of vaccine preventable childhood diseases by between 95% and 100% depending on disease reinforcing the importance of continued vaccination.

1.1.2 Government Involvement in Vaccines

Other than the licensure of vaccines for use in the United States (U.S.), a process governed by the Food and Drug Administration (FDA), the federal government does not
regulate the vaccination of children. The main focus of the federal government is to make recommendations and provide funding to ensure high levels of vaccination coverage throughout the country. Vaccine policy recommendations, including a recommended schedule for vaccine administration, are made by the Department of Health and Human Services which is advised by five expert committees. The two primary committees responsible for making recommendations regarding vaccinations are the Advisory Committee on Immunization Practices (ACIP) and the National Vaccine Advisory Committee (NVAC) (Organization chart depicted in Appendix 2).

The ACIP determines which FDA licensed vaccines will be added to the recommended schedule for children and adults. Recommendations given by the ACIP reflect a number of considerations, chiefly safety, effectiveness and the cost-benefit ratio, among others. The ACIP is under the purview of the CDC and publishes recommendations in the Morbidity and Mortality Weekly Report (MMWR). Recommendations are updated every three to five years or when necessary as new vaccines are licensed for use in the U.S. or if issues arise with the current schedule. The ACIP recommendations specify the age, number of doses and interval between dosing, precautions and contraindications, and whether the vaccine will be federally funded by the vaccines for children program (VFC).

The NVAC makes recommendations on areas such as vaccine research, safety, and financing. The responsibilities of NVAC include: ensuring adequate supply of safe and effective vaccines, developing research priorities, and identifying areas of government and non-government cooperation regarding immunization throughout the
country. The NVAC makes recommendations to the National Vaccine Program director, which also monitors vaccine safety\textsuperscript{3,5,10}.

Funding for vaccines and vaccine administration is provided mostly through the Vaccination Assistance Act (section 317), passed by Congress in 1962\textsuperscript{4}. Originally designed to be a onetime appropriation of funds to help states implement mass immunization campaigns by providing grants for vaccines and personnel, section 317 has been continuously reauthorized since its implementation\textsuperscript{4}. Concerns regarding the vaccination of vulnerable children, particularly those of low socio-economic status, sparked the implementation of the Vaccines for Children (VFC) program in 1993\textsuperscript{11}. This act specifically provides vaccines, not funding, for children under 19 years of age who are Medicaid-eligible, Alaskan native or American Indian, or under-insured and cared for by a federally qualified health center. States can supplement this funding to expand coverage to other groups of children\textsuperscript{4,11}.

The authority to protect against dangers to public health is a right afforded to individual states by the U.S. Constitution\textsuperscript{5,12}. While states can vary in the type and number of vaccines required, as well as the rules regarding exemptions, currently all states and the District of Columbia have laws regulating vaccination upon entry into a licensed or regulated program (e.g. schools and daycares)\textsuperscript{13}. The enactment of laws requiring vaccination for entry into daycare or school has had a significant positive impact on vaccine coverage\textsuperscript{14-16}. 
1.1.3 Safety and Monitoring of Vaccines

Vaccines are subject to the same clinical trial regimen as other prescription medications and biologics, a process of evaluation used to determine safety and efficacy. Vaccines also undergo post-licensure surveillance to detect rare side effects not seen among clinical trial participants. These phase IV trials are done via large linked databases such as the Vaccine Adverse Event Reporting System (VAERS), of the Vaccine Safety Datalink (VSD) Project. The management of safety and monitoring of vaccine falls under the purview of the National Vaccine Program which was formed as part of the National Childhood Vaccine Injury Act (NCVIA) in 1986 to provide safety monitoring as well as injury compensation for adverse vaccine events (Compensation Events listed in Appendix 1).

There are several systems in place to monitor adverse events potentially related to vaccination. Created in 1990, VAERS is a collaborative effort by CDC and FDA to create a single monitoring system for adverse events. This passive monitoring system is populated by reports of mild to severe adverse events from health professionals, vaccine manufacturers, and the general public. In 1990, the CDC also created the VSD Project which utilizes information from 10 managed care organizations to monitor vaccine safety. The participating managed care organizations track all vaccinations administered, allowing for large scale safety studies and hypothesis testing. To understand adverse events at the individual level the Clinical Immunization Safety Assessment Network (CISA) evaluates persons who have experienced adverse events following vaccination. This information helps develop protocols for health care providers when faced with similar events in the future. The information gathered from monitoring programs, such as
those described, is used to determine vaccine injury compensation related to adverse events following vaccination\textsuperscript{17,18,20}.

The NCVIA was passed in response to increasing concerns over the safety of vaccines, particularly related to the diphtheria, tetanus and whole cell pertussis (DTP) vaccine\textsuperscript{17,19-21}. Public health officials were concerned that increasing liability disputes with vaccine manufacturers would negatively impact vaccine supply. In other words, the cost of defending against litigation might force vaccine manufacturers to leave the market and discontinue research and development of vaccines, itself a very costly endeavor over a long development timeline. Subsequently, the NCVIA established the Vaccine Injury Compensation Program (VICP) which compensates individuals who experience adverse vaccine events listed in the Vaccine Injury Table\textsuperscript{19}. The vaccine injury table provides a description of specific adverse events and time frames for which individuals can file a claim for compensation. The events listed in the vaccine injury table are not identified as causal events, but events where evidence supports an association between vaccination and the adverse event\textsuperscript{19-21}. Those who receive compensation via the VICP waive their right to file a claim against the vaccine manufacturer. The list is updated by the Secretary of the Department of Health and Human Services to reflect the current science surrounding all recommended childhood vaccines\textsuperscript{20,21}.

1.1.4 Vaccine Recommendations in the United States

1.1.4.1 History of Vaccine Recommendations by Non-governmental Organizations

Beginning in the 1940s, government groups and physician associations, such as the American Academy of Pediatrics (AAP) and the American Academy of Family
Practices (AAFP), began creating and distributing recommended vaccine schedules for children. Early schedules included vaccines to prevent diseases such as small pox, diphtheria, tetanus, pertussis, polio, measles, mumps, and rubella. In the 1980’s small pox was declared eradicated in the U.S., thus ending recommendations for the administration of small pox vaccines to U.S. children. In 1995, the AAP and AAFP joined with the Advisory Committee on Immunization Practices (ACIP) to create a unified schedule distributed by the CDC, a schedule that is still produced today.

1.1.4.2 Current Vaccine Recommendations

The number of recommended vaccines has expanded as new vaccines have become commercially available to treat prevalent diseases. In 2012, the recommended schedule for children younger than six included vaccines against hepatitis A and B (Hep A and Hep B), rotavirus, diphtheria, tetanus, pertussis, Haemophilus influenzae type b (Hib), pneumococcal, poliovirus, measles, mumps, rubella, varicella, and influenza. Given the increase in the number of vaccines on the CDC recommended schedule, it has become an important tool to assist both physicians and parents.

To reduce the number of injections and help ease the burden of keeping children on schedule, vaccine manufacturers have created combination vaccines. These combination vaccines contain antigens for more than one disease. Routine combinations such as the measles, mumps, and rubella (MMR) vaccine, and the diphtheria, tetanus, and acellular pertussis (DTaP) are widely used. However, other combination vaccines include up to five individual vaccines, such as Pediarix®, which combines the DTaP, HepB, and inactivated poliovirus (IPV) vaccines, and Pentacel®, which combines the DTaP, Hib, and IPV vaccines. The recommended schedules do not promote one
vaccine over another but indicate that the use of combination vaccines can ease the burden on physicians to keep track of vaccine scheduling and maximize coverage \cite{25,27,28}. Appendix 3 shows the current 2012 CDC published immunization schedule recommended by the ACIP.

1.1.5 Individual Disease-Vaccine Profiles

1.1.5.1 Inactivated Polio Vaccine

1.1.5.1.1 Epidemiology Overview – Poliomyelitis

1.1.5.1.1.1 Organism

Poliovirus, from the family \textit{Picornaviridae}, is a human enterovirus stable at low pH values. The poliovirus is a single-stranded RNA virus with a non-enveloped icosahedral protein coat. There are three poliovirus serotypes (P1, P2, and P3) and immunity to one serotype confers little to no immunity to the other two serotypes. Poliovirus is easily inactivated with heat, chlorine, formaldehyde, or ultraviolet light \cite{29}.

1.1.5.1.1.2 Pathogenesis

Poliovirus is passed most often via fecal-oral transmission. However, oral transmission is also possible due to infection of the pharynx. After entering the body through the mouth, poliovirus invades cells in the pharynx and gastrointestinal tract. From these initial implantation sites the virus is able to invade local lymph tissue and then spread systemically. Invasion of central nervous system tissue in the spinal column and brain stem result in spinal and bulbar paralysis. While the virus is present in the throat for only a short period of time, approximately one week, shedding of the virus
from the gastrointestinal tract can last several weeks. Shedding of viral particles begins before onset of symptoms.

1.1.5.1.1.3 Incidence before and after introduction of Poliovirus vaccine

The first outbreak of poliomyelitis in the U.S. was described in 1843 and incidence increased to a peak of over 21,000 paralytic cases in 1952. The first vaccine, IPV, was licensed in 1955, and the oral polio vaccine (OPV) was licensed in 1961. The year OPV was licensed, only 161 cases of paralytic polio were reported in the U.S., marking a dramatic reduction in morbidity in less than a decade. The last wild-type paralytic polio case acquired in the U.S. was documented in 1979, however, imported and vaccine-associated cases continued.

A total of six imported cases of polio were reported in the U.S. between 1980 and 1993. In the U.S. 144 cases of vaccine-associated paralytic polio (VAPP) were reported between 1980 and 1999. During this 20-year period, two indeterminate cases of paralytic polio occurred, but no poliovirus was recovered. Because the majority of U.S. polio cases were vaccine-associated, ACIP recommended discontinuing the use of OPV in 2000 favoring the IPV-only schedule. In 2005, one documented case of VAPP was reported in an unvaccinated U.S. citizen who had traveled to Costa Rica and come in contact with OPV vaccinated individuals.

1.1.5.1.1.4 Risk Factors

While there is no endemic polio in the U.S., unvaccinated persons are at risk for both wild-type polio (Types 1 and 3) and VAPP when traveling to other countries. In 2012, cases of wild-poliovirus (WPV) have been reported in Nigeria, Pakistan,
Afghanistan, and Chad. Circulating VAPP has been reported in Nigeria and the Democratic Republic of Congo although more countries reported cases in 2011. Several risk factors for progressing to paralytic poliomyelitis have been reported. The risk for paralytic poliomyelitis increases with age and the following risk factors: being infected with a larger amount of poliovirus, receiving intramuscular injections while infected, participating in strenuous exercise, having had a tonsillectomy, and being pregnant.

1.1.5.1.5 Clinical Presentation

The most recognized symptom of poliomyelitis, flaccid paralysis, occurs in less than 1% of cases. Those cases progressing to flaccid paralysis usually begin with symptoms that can include sore throat, fever, nausea, vomiting, abdominal pain, constipation, diarrhea or influenza-like illness followed by stiffness in the neck and back leading to spinal, bulbar, or bulbospinal paralysis. Spinal paralysis is most common, usually causing asymmetric paralysis that most often affects the legs.

Paralysis usually peaks within 3-4 days of onset, and while some of the occurring paralysis may abate, any remaining paralysis after 1 year can be considered permanent. Among paralytic cases, death is the result in approximately 2% to 5% of children and 15% to 30% of adults. The risk of death significantly increases to 25% to 75% with bulbar paralysis.

Non-paralytic aseptic meningitis occurs in approximately 1% of cases and causes stiffness of the neck, back and/or legs lasting 2 to 10 days followed by complete recovery. Symptoms of non-paralytic aseptic meningitis follow a period of minor illness similar to that of paralytic cases but never progress to paralysis.
It is thought that over 90% of cases of poliomyelitis are asymptomatic or result in mild non-specific symptoms \( ^{29} \). The relative proportion of paralytic vs. unapparent/asymptomatic illness can range anywhere from 1 in 50 to 1 in 1,000 \( ^{34} \). Symptomatic cases can range from influenza-like illness or respiratory problems to gastrointestinal disturbances and are most often indistinguishable from other viral illness \( ^{29} \).

Post-polio syndrome, a progressive weakening of muscles over time following recovery, occurs among a small percentage of patients. The syndrome is not associated with re-infection \( ^{39} \).

### 1.1.5.1.2 Inactivated Polio Vaccine

#### 1.1.5.1.2.1 History

The first licensed vaccine was Jonas Salk’s IPV in 1955, followed by licensure of Type 1 and Type 2 OPVs in 1961 and Type 3 OPV in 1962 \( ^{30} \). A trivalent OPV was licensed in 1963 \( ^{30} \), and an enhanced IPV with greater efficacy was licensed in 1987 \( ^{40;41} \).

Prior to 1997, ACIP developed three schedules for vaccination against poliovirus: OPV-only, IPV-only, and IPV-OPV combination \( ^{42} \). In 1997, in order to reduce VAPP, ACIP recommended switching to a schedule which included two doses of IPV followed by two doses of OPV as an intermediary step to eliminating OPV from the current recommendations \( ^{43} \). In 2000, due to the eradication of wild-type polio in the U.S. and disease risk associated with OPV, ACIP recommended the discontinuation of the use of OPV \( ^{34} \).
1.1.5.1.2.2 Licensure and Production

While currently two IPVs are licensed in the U.S., IPOL® and POLIOVAX®, only IPOL is currently available on the market 35. IPOL was licensed to Institut Merieux in 1989 for use in infants and adults to prevent poliomyelitis. The single dose sterile suspension contains 40 D antigen units of Mahoney type 1, 8 D antigen units of MEF-1 type 2, and 32 D antigen units of Saukett type 3 viruses. Each dose also contains 0.5% of 2-phenoxyethanol and up to 200 ppm of formaldehyde as preservative. To create the vaccine, virus is grown in Vero cells using the microcarrier method. After concentration, purification, and formaldehyde inactivation the vaccine may contain trace amounts of neomycin, streptomycin, and polymyxin B from the production process 34.

1.1.5.1.2.3 Efficacy and Effectiveness

While mucosal immunity is induced with the use of IPV, it is less immunogenic in the mucosa than OPV 44-46. Studies indicate that after three doses, antibodies are induced in 99% of infants against Type 1 poliovirus, and 100% of infants against Type 2 and Type 3 poliovirus 40;41;44. The vaccine is efficacious after just two doses with 94% responding to Type 1 and 100% responding to Type 2 and Type 3 40;41. Long term effectiveness using IPV has also been demonstrated 47. Despite the decreased mucosal immunity, the sustained eradication of poliomyelitis in the U.S. indicates continued effectiveness with the use of only IPV 48.

1.1.5.1.2.4 Safety

The most noted systemic reaction following IPV injection was fever over 100.6°F which occurred in 7% of children after dose 1, 12% of children after dose 2, and 4% of
children after dose 3\(^\text{34}\), however, IPV was evaluated at the same time as DTwP (whole cell pertussis vaccine) and thus not all systemic reactions can be attributed to IPV. In fact, as will be noted later, DTwP is associated with fever\(^\text{34,49}\). An Institute of Medicine (IOM) study indicated that there was no increased risk for serious adverse events when using an IPV-only schedule\(^\text{34,49}\) which is echoed by studies in other countries\(^\text{50,51}\).

Contraindications for vaccination with IPV include persons who experience allergic reaction to a previous dose or to the antibiotics streptomycin, polymyxin B, or neomycin. Women who are pregnant are advised not to receive IPV unless they are at risk for infection during pregnancy. There are no contraindications for immunodeficient children or breastfeeding children\(^\text{35}\).

Since October 1, 1988, 276 claims have been filed with the NVICP, including 14 deaths as of July 2, 2012; of these, seven were compensated\(^\text{52}\). The NVICP vaccine injury table lists anaphylaxis within four hours as being the only covered condition arising from vaccination with IPV (Appendix 1Table 1, Table 2)\(^\text{52}\).

1.1.5.1.2.5 Specific Vaccine Recommendations

The IPV schedule is a four-dose series at 2 months, 4 months, 6-18 months, and 4-6 years\(^\text{25}\). The first dose should be given after 6 weeks and the last dose needs to be given after 48 months of age. The minimum interval between doses 1 and 2 and doses 2 and 3 is 4 weeks and the minimum interval between doses 3 and 4 is 6 months\(^\text{53}\). Due to similarity in scheduling among several vaccines, the use of combinations in accordance with their FDA approvals is neither prohibited nor specifically recommended by ACIP\(^\text{25,27}\) (see section 1.1.5.7 on combination vaccines).
1.1.5.2 Diphtheria Tetanus and Pertussis

1.1.5.2.1 Epidemiology Overview – Diphtheria

1.1.5.2.1.1 Organism

Diphtheria is caused by *Corynebacterium diphtheriae*, an aerobic gram-positive bacillus bacteria which can be either nontoxigenic or toxigenic. Of the four biotypes of *C. diphtheria*—gravis, mitis, intermedius, and belfanti—gravis is associated with the most severe disease. Nontoxigenic biotypes cause sore throat or infective endocarditis. Toxigenic biotypes are formed when a bacteriophage lysogenizes *C. diphtheriae* with the tox gene. These toxigenic bacteria are associated with severe disease.29

1.1.5.2.1.2 Pathogenesis

After infecting the nasopharynx, the diphtheria toxin in toxigenic forms moves begins to inhibit cellular protein synthesis and cause local tissue destruction. The toxin is then absorbed through the membrane site and is carried to other tissues within the body via the bloodstream. As the toxins enter other tissues, myocarditis, neuritis, thrombocytopenia, and proteinuria can occur. Non-toxin producing strains have the same pathogenesis without the toxin-mediated tissue destruction.29,54,55

1.1.5.2.1.3 Incidence before and after vaccine introduction

In the 1920s, during development of the diphtheria toxoid, the incidence of diphtheria in the U.S. was about 140-150 cases of diphtheria per 100,000 population, or approximately 100,000 to 200,000 cases per year and between 13,000 and 15,000 deaths.54-56 With the introduction of diphtheria toxoid, cases declined to about 15 per 100,000
persons by 1945. Three decades later, during the 1970’s, the number of reported annual cases had declined to 196 cases. In 1980, reporting requirements changed and nontoxigenic cutaneous isolates were no longer reported. Between 1980 and 2004, a total of 57 U.S. cases were reported. In 2009, there were no U.S. cases of diphtheria reported.

1.1.5.2.1.4 Risk Factors

Native Americans and those with lower socioeconomic status, particularly the homeless, are at increased risk for diphtheria. Prior to vaccine introduction, diphtheria was most common among those under five years of age or those over 40 years of age. Currently, those over 40 and under immunized persons are at increased risk of disease. Diphtheria boosters are recommended every 10 years to maintain adult immunity.

1.1.5.2.1.5 Clinical Presentation

The general incubation period for diphtheria is 2 to 5 days but can be as little as 1 day or as many as 10 days. Complications from diphtheria include: myocarditis, sometimes occurring weeks after illness; neuritis, including paralysis of the soft palate, eye muscles, limbs, and diaphragm, the latter of which can lead to secondary pneumonia. Death occurs in approximately 5% to 10% of cases; risk of death increases for those under 5 or over 40 years. The disease is classified according to the site where the membrane forms and can include the nasopharynx, eyes, or vulvovaginal area.

Anterior nasal diphtheria presents similarly to the common cold, although the nasal discharge can become blood tinged as a white membrane forms on the nasal
septum. This presentation of diphtheria is often milder due to poor systemic distribution of toxin from this location. Pharyngeal or tonsillar diphtheria is the most common presentation of the disease. Initially, pharyngeal or tonsillar diphtheria presents with malaise, sore throat, anorexia, and low grade fever. A bluish-white membrane will then form and extend to cover anywhere from a small patch to the entire soft palate and tonsils within two to three days. As toxin is absorbed patients can develop severe prostration, striking pallor, rapid pulse, stupor and/or coma. Death can occur within six to ten days. Patients with pharyngeal diphtheria may also develop “bullneck” which is caused by edema of the submandibular areas of the anterior neck.

Laryngeal diphtheria presents with fever, hoarseness, and barking cough. The formation of the membrane can lead to airway obstruction, coma, and death. Occasionally, pharyngeal diphtheria can extend to the larynx.

Cutaneous diphtheria is more often associated with non-toxigenic strains and can account for increased immunity in some tropical areas where infections are common. Skin infections with toxigenic strains are also less severe. The skin ulcer caused by the infection and membrane formation can also harbor other infectious particles.

1.1.5.2.2 Epidemiology Overview – Tetanus

1.1.5.2.2.1 Organism

Tetanus is caused by the exotoxin produced by the bacterium Clostridium tetani. This gram-positive anaerobic rod is sensitive to heat and the presence of oxygen.
Spores of *C. tetani* are found in manure enriched soils and the intestines of most pets and farm animals. The bacterium develops a terminal spore which is very resistant to heat and antiseptics; they survive autoclaving for 10-15 minutes and exposure to phenol and other chemicals \(^{29}\).

Exotoxin production by *C. tetani* comes in two forms tetanolysin and tetanospasmin. The function of the first, tetanolysin, is not well known. The function of tetanospasmin is mostly neurologic producing rigidity and convulsive spasms of the skeletal muscles. Lockjaw, a rigidity of the jaw and neck, is most commonly associated with *C. tetani* infection. Tetanospasmin is one of the most potent toxins with a lethal dose of 2.5ng per kg \(^{29,60}\).

### 1.1.5.2.2.2 Pathogenesis

Introduction of *C. tetani* into the body is usually through a contaminated wound. As the spores germinate, toxins are produced and disseminated to sites in the central nervous system via the blood and lymphatic system. The characteristic muscle spasms and contractions are caused by interference with the release of neurotransmitters \(^{29,60}\).

### 1.1.5.2.2.3 Incidence before and after vaccine introduction

It is indicated that deaths from tetanus were on the decline from 1900 to the introduction of tetanus toxoid in the 1940s \(^{56}\), potentially due to better hygiene and understanding of disease transmission. When the toxoid was introduced, the annual incidence was approximately 0.4 cases per 100,000 population, equating to about 500-600 cases \(^{56}\). From the mid-1970s to 2000, approximately 0.05 cases per 100,000
population occurred each year\textsuperscript{59,61} and the case fatality declined from 30\% to 10\%\textsuperscript{59,61}.

In 2008, 18 cases of tetanus were reported in the U.S.\textsuperscript{62}.

**1.1.5.2.2.4 Risk Factors**

Tetanus is most often associated with puncture wounds due to the anaerobic environment needed for \textit{C. tetani} proliferation\textsuperscript{54,55}. However, recently tetanus has been increasingly associated with any type of wound including surgery, burns, crush wounds, otitis media, dental infections, animal bites, abortions, and pregnancy. Between 1996 and 2000, the burden of disease shifted from those over 40 years to those under 40 years of age. This shift is thought to be associated with increased disease among injection drug users, particularly heroin\textsuperscript{61}.

**1.1.5.2.2.5 Clinical Presentation**

The incubation period for tetanus is about 8 days but can vary between 3 and 21 days, often dependent upon how far from the central nervous system the infected wound occurs. Shorter incubation periods are often correlated with higher risk of death. There are three clinical groupings of tetanus. The most common, accounting for approximately 80\% of cases is generalized tetanus. Generalized tetanus usually presents in a descending pattern often starting with lockjaw. This form of tetanus may also be accompanied by fever, sweating, high blood pressure, episodic rapid heart rate, and spasms lasting 3 to 4 weeks\textsuperscript{29,60}. Full recovery may take months. Generalized tetanus may also occur in newborns from 4 to 14 days of age. Usually starting in the umbilical cord, neonatal general tetanus occurs among infants of unimmunized mothers due to a lack of passive immunity\textsuperscript{54,63}. Case fatality from generalized tetanus is approximately 18\%\textsuperscript{54}. 
A rare form of tetanus, cephalic tetanus, is associated with otitis media and cranial injuries. Cephalic tetanus usually involves the cranial nerves, particularly those in the facial area.\textsuperscript{58}

Local tetanus, consisting of localized contractions around the wound site, is extremely rare. It is thought that in some cases tetanus may begin as local and then progress to general tetanus. Local tetanus has the lowest case fatality at less than 1\%\textsuperscript{29,56}.

1.1.5.2.3 Epidemiology Overview – Pertussis

1.1.5.2.3.1 Organism

Pertussis, also known as whooping cough, is caused by the bacterium \textit{Bordatella pertussis}, a small gram negative aerobic rod. The clinical features of \textit{B. Pertussis}, particularly the characteristic whoop when coughing, are caused by multiple antigenic sites and biologically active materials, particularly pertussis toxin.\textsuperscript{29} Antibodies to any single antigenic site are enough to prevent infection; however, the immune response produced through both infection and vaccination is not permanent and a booster is necessary to maintain immunity.\textsuperscript{29,60}

1.1.5.2.3.2 Pathogenesis

Pertussis is a respiratory disease primarily mediated by toxin production. Transmission is usually person to person via respiratory droplets. Persons with pertussis are most contagious during the catarrhal and early paroxysmal phase of illness. The production of pertussis toxin after colonization of the bronchial tubes paralyzes the cilia, inhibiting pulmonary secretions. The toxin produced has systemic effects other than
coughing, including lymphocytosis. *Bordetella pertussis* rarely invades other tissues but has been isolated from macrophages in some clinical studies\(^{29,60}\).

### 1.1.5.2.3.3 Incidence before and after vaccine introduction

Between 1940 and 1945 incidence was about 150 cases per 100,000 population, an average of approximately 175,000 cases of pertussis each year\(^55\). The introduction of the whole cell pertussis vaccine in the 1940s was followed by a decline in the yearly average number of cases. By 1960, the annual incidence had dropped to just 8 cases per 100,000 population and continued fall\(^{54,55}\). During the 1980s, annual incidence had declined dramatically to 1 case per 100,000 population or an average of 2,900 cases a year\(^{54,55}\). This was the nadir, though. From this point, the average annual incidence began to increase again. By 2004, the annual incidence exceeded 25,000 cases\(^55\). By September of 2012, the national incidence was up to 9.3 cases per 100,000 population, representing the continuation of an outbreak which began in 2010 and caused the death of at least 10 infants\(^{57,64}\).

### 1.1.5.2.3.4 Risk Factors

All persons with inadequate immunity, either due to lack of vaccination or waning immunity, are susceptible to pertussis. Older children and adults often present with milder symptoms and are sometimes asymptomatic. Infants under three months, those too young to be vaccinated, are at increased risk for serious sequelae, including pneumonia and neurologic complications resulting from lack of oxygen and/or toxin \(^{29}\).
1.1.5.2.3.5 Clinical Presentation

The average incubation period for pertussis is 7 to 10 days but periods as short as 4 days and as long as 42 days have been reported. Disease is categorized into three stages. The first (catarrhal) stage includes runny nose, sneezing, low grade fever, and occasionally a mild cough. Diagnosis usually occurs during the second (paroxysmal) stage, characterized by the well-known whooping cough which occurs in short episodes. The second stage usually lasts one to six weeks, during that time coughing episodes increase during the first weeks and then decrease over time. The final (convalescent) stage, can last for two to three weeks. However, the paroxysms can occur for many months with subsequent respiratory illness 29,60.

1.1.5.2.4 Diphtheria, Tetanus, and acellular Pertussis vaccine development: DTP and DTaP

1.1.5.2.4.1 History

While the toxoids for diphtheria and tetanus and the whole cell pertussis vaccine were developed separately, they have been most commonly administered together. The first diphtheria, tetanus, and whole cell pertussis (DTP) vaccine was created in the 1940s. While diphtheria and tetanus can be given separately as the DT vaccine, it was estimated that in 1993 about 98% of those vaccinated with diphtheria, tetanus and pertussis were receiving DTP 58. Beginning in 1991, the formulation switched from whole cell (DTP) to acellular pertussis (DTaP) to reduce the incidence of side effects 58.
1.1.5.2.4.2 Licensure and Production

Currently three DTaP vaccines and four combination vaccines including DTaP are available for use among infants in the U.S. (See Combination Vaccine Section 1.1.5.7). For infants unable to receive acellular pertussis, a generic DT vaccine is also available 57.

Tripedia®, produced by Sanofi Pasteur, was approved in July 1996 for the initial four doses of DTaP among children aged six weeks to six years. The diphtheria and tetanus components are obtained from Corynebacterium diphtheria grown in modified Meuller and Miller medium and Clostridium tetani grown in a peptone-based medium with bovine extract. The toxins from both cultures are detoxified using formaldehyde and purified separately using serial ammonium sulfate fractionation and diafiltration, then adsorbed using aluminum potassium sulfate. The acellular pertussis component is obtained from culture fluids of Bordetella pertussis grown in a modified Stainer-Scholte medium and purified using salt precipitation, ultracentrifugation, ultrafiltration, and inactivated using formaldehyde. The diphtheria and tetanus toxoids are combined with the pertussis concentrate. Each dose contains 6.7 Lf (limit of flocculation units) of diphtheria toxoid, 5 Lf of tetanus toxoids, and 46.8 mcg of pertussis antigens. There are no more than 50 endotoxins per 1 mL. Each dose also contains 0.170 mg of aluminum, 100 µg of residual formaldehyde, gelatin, and polysorbate 80 65.

Daptacel®, also produced by Sanofi Pasteur, was licensed in 2002 and the production methods are similar to Tripedia. Each dose of Daptacel contains 15 Lf diphtheria toxoid and 5 Lf tetanus toxoid. Each dose also contains multiple pertussis antigens including 10 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin, and 5 mcg fimbriae types 2 and 3. Other
ingredients include 1.5 mg aluminum phosphate, 5 mcg formaldehyde, 50 ng glutaraldehyde, and 3.3 mg 2-phenoxyethanol. 

Infanrix®, produced by GlaxoSmithKline and licensed in 1997, uses a different production method from the Sanofi Pasteur DTaP vaccines. While the purification process is similar, Infanrix uses Corynebacterium diphtheriae cultured in Fenton medium with bovine extract and Clostridium tetani cultured in a modified Latham medium derived from bovine casein. The PT and FHA from Bordetella pertussis are isolated from a fermentation broth of a modified Stainer-Scholte liquid medium. Pertactin is extracted using a heat treatment. All antigens are purified using a chromatographic and precipitation process and then PT is detoxified using glutaraldehyde and formaldehyde while FHA and pertactin are treated with just formaldehyde. Each dose contains 25Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of PT, 25 mcg of FHA, and 8 mcg of pertactin. Doses also contain 0.625 mg aluminum hydroxide, 4.5 mg sodium chloride, 100 mcg formaldehyde and 100 mcg polysorbate 80.

1.1.5.2.4.3 Efficacy and Effectiveness

All three DTaP vaccines indicate that after three doses, efficacy for diphtheria and tetanus toxoids is 100%. For Tripedia, post-trial efficacy is 77% for all culture-proven cases of pertussis and 92% for culture-proven cases with a cough lasting more than 30 days. Daptacel found an efficacy of 77% for all laboratory-confirmed cases and 84% for all laboratory-confirmed cases with cough over 21 days. The efficacy for Infanrix found only 71% for all laboratory-confirmed cases and approximately 84% for cases with a cough lasting over 21 days. All studies show similar efficacy despite differences in end points, thus indicating that no one vaccine is more effective than the other.
1.1.5.2.4.4 Safety

The safety profiles for all three DTaP vaccines are similar. About 20% to 40% of children experience pain, redness, and/or swelling at the injection site; this percentage increases for the fourth and fifth dose\(^5\). Other reactions include fever (3%-5%), fatigue and irritability. Approximately 1 in 10,000 doses will result in a more severe reaction including fever of 105°F, febrile seizure, persistent crying over three hours, and hypotonic/hyporesponsive episodes\(^5\). However, these reactions are less severe and less frequent than those associated with DTP. Very rarely, severe systemic reactions such as brachial neuritis, Guillain-Barre syndrome, or anaphylaxis occurs\(^5\). The NVICP indicates that among vaccines containing tetanus toxoid, anaphylaxis occurring within 4 hours and brachial neuritis occurring within 2 to 28 days are covered. For vaccines containing pertussis, anaphylaxis occurring within 4 hours and encephalopathy within 72 hours are covered events\(^19,20\) (Appendix 1, Tables 1, 2).

1.1.5.2.4.4 Specific Vaccine Recommendations

Infants under 1 year are recommended to receive three doses of DTaP at 2, 4, and 6 months of age. Contraindications to DTaP include severe allergic reaction or encephalopathy occurring within 7 days of any vaccination. Several precautions within the preceding 48 hours are also mentioned, including moderate or severe acute illness, temperature over 105°F, collapse or shock-like state, persistent crying over 3 hours, and convulsions\(^25\).
1.1.5.3 Hepatitis B

1.1.5.3.1 Epidemiology Overview – Hepatitis B

1.1.5.3.1.1 Organism

The hepatitis B virion (HBV) is part of the Hepadnaviridae family; HBV is a small double-shelled virus with a circular, partially double-stranded DNA genome. Hepatitis B virus has several antigenic targets including hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). The HBsAg antigenic site is an effective immunogen in hepatitis B vaccines and one of several markers of infection.

1.1.5.3.1.2 Pathogenesis

The hepatitis B virus is carried in the blood and serous fluids. Trace amounts of virus can also be found in saliva and semen. Exposure of the mucosal surfaces or injection into the body of infectious fluids allows HBV to enter the bloodstream where it is transported to the liver and viral replication occurs. The progression of infection is measured through the levels of the antigenic compound HBsAg and corresponding antibodies to HBsAg (Anti-HBs) and HBcAg (Anti-HBc).

1.1.5.3.1.3 Incidence and Prevalence

Due to the increased availability of tests to differentiate between types of hepatitis, hepatitis B became reportable as a separate entity in the 1970s. Incidence of hepatitis B peaked in the mid-1980s, around the time of the introduction of the recombinant vaccine in 1986, with an estimated 26,000 cases per year. Initial declines in the late 1980s and early 1990s were attributed to HIV prevention efforts as HBV and HIV have similar modes of transmission. Between 1990 and 2004, reported
incidence of acute hepatitis declined from 8.5 to 2.1 cases per 100,000 population. This decline in incidence was greater among children less than 12 years of age where reported acute cases fell from 1.1 to 0.36 cases per 100,000 population. While children younger than 10 years of age account for less than 10% of incident acute hepatitis B cases, they are associated with 30% to 40% of chronic hepatitis B cases.

Those who are infected with hepatitis B run the risk of progressing to chronic infection, the risk for which is inversely associated with age. Although the overall risk for progression from acute to chronic hepatitis B infection is approximately 5%, the risk for infants and children ages 1 to 5 years is much higher (90% and 30-50%, respectively). Between 1988 and 1994 the National Health and Nutrition Examination Survey (NHANES) estimated that the overall age-adjusted prevalence of HBV was 4.9% (including chronic and previous infection). In 2001, the CDC estimated between 700,000 and 1.1 million persons in the U.S. had chronic hepatitis B infection. Additionally 5,000 to 8,000 persons become chronically infected each year.

1.1.5.3.1.4 Risk Factors

Risk factors for infection with hepatitis B as an adult include emigrating from endemic countries, injection drug use, male homosexual activity, hemodialysis, household contact with hepatitis B-positive persons, multiple partners, male prisoners, health care providers, and clients and staff of mental health institutions. Risk factors for infants and children include household members who are hepatitis B-positive, particularly infants born to positive mothers due to perinatal transmission.
1.1.5.3.1.5 Clinical presentation

Asymptomatic acute hepatitis B infection is common and occurs most often among infants and children. It is estimated that approximately 50% of adults have asymptomatic acute infections. Symptoms differentiate into prodromal, icteric, and convalescent phases. The prodromal phase, lasting from three to ten days, is nondescript and can include symptoms such as malaise, anorexia, nausea, vomiting, fever, headache, myalgia, right upper quadrant pain, and dark urine. The icteric phase usually lasts from one to three weeks and is characterized by jaundice, light or gray stools, hepatic tenderness, and hepatomegaly. Finally, the convalescent phase is marked with the disappearance of jaundice, anorexia and other symptoms; however, malaise and fatigue may persist for weeks to months after infection. In adults, 95% of cases result in complete recovery and lasting anti-HBs immunity.

1.1.5.3.2 Hepatitis B Vaccine

1.1.5.3.2.1 History

In the U.S., the first hepatitis B vaccine was licensed in 1981. This plasma-derived vaccine contained purified HBsAg particles from chronically infected humans. While safe and effective, the use of human blood product to make the vaccine led to low vaccine uptake and the plasma-derived vaccine was removed from the market in 1992. In mid-1986, a recombinant hepatitis B vaccine was licensed in the U.S.; currently two licensed recombinant vaccines are available for use in infants.

1.1.5.3.2.2 Licensure and Production

Engerix-B® is a recombinant hepatitis B vaccine licensed to SmithKline Biologicals in July of 1998. To develop this vaccine, a functional plasmid containing the S gene of hepatitis B
adw2 is introduced into *Saccharomyces cerevisiae*. After fermentation *S. cerevisiae* is disrupted and solids are precipitated and cleaned using diafiltration. Purification using gel permeation chromatography, ion exchange chromatography, and CsCl gradient ultracentrifugation is performed to concentrate the HBsAg protein. The pediatric dose contains 10 mcg antigen protein adsorbed onto 0.25 mg aluminum hydroxide84.

Recombivax HB®, licensed in 1999 to Merck & Co., Inc., is produced similarly to Engerix-B. The pediatric formulation contains 5 mcg surface antigen, 0.5 mg aluminum hydroxide, and less than 15 mcg/ml residual formaldehyde85.

1.1.5.3.2.3 Efficacy and Effectiveness

Clinical trials of Engerix-B found that sero-protection was 93%-97% dependent on spacing between doses. Sero-protection was higher for neonates on a 0, 1, 6 month schedule. The sero-protection of children age 1 to 10 years was 98%. Only 3% of vaccinated neonates born to mothers who were carriers of HBsAg and HBeAg, and who did not receive hepatitis B immunoglobulin (HBIG), became chronic carriers compared to 60-90% of non-vaccinated children84;86.

Trials with Recombivax HB indicated that 100% of infants had protective antibody levels after three doses of vaccine85. Among vaccinated children born to HBV-positive mothers, 96% were HBV free at nine months of age81. This study administered HBIG in combination with Recombivax HB and the results indicate that HBIG does not decrease the immune response associated with hepatitis B vaccination at birth72.

1.1.5.3.2.4 Safety

Hepatitis B vaccination is contraindicated in cases where persons have an allergy to a known vaccine component, including yeast, or a previous serious reaction to vaccination24.
Pregnancy and immune suppression are not contraindications to vaccination. Limited post-marketing surveillance data on the history of \textsuperscript{24,76,77,79} 

Approximately three to nine percent of children experience pain at the injection site following vaccination. Fatigue, headache, and irritability have been reported in 0 to 20% of children and fever is reported in 0.45 to 6.4% of children dependent on the clinical trial in question \textsuperscript{85-88}. Serious systemic reactions, including allergic reactions, are rare; however, vaccination is contraindicated in children who experienced previous systemic reactions \textsuperscript{85,86}. While not reported for children, early reports indicated that several adverse events were associated with Hepatitis B vaccination in adults including: anaphylaxis, multiple sclerosis, chronic fatigue syndrome, neurologic disorders, rheumatoid arthritis, type 1 diabetes, and autoimmune disease \textsuperscript{49,86,88,89}. While 1.1 cases of anaphylaxis per million doses of vaccine are attributed to hepatitis B vaccination, no causal association between vaccination and other chronic conditions could be determined\textsuperscript{24}.

\textbf{1.1.5.3.2.5 Specific Vaccine Recommendations}

Early recommendations targeting high risk individuals were not successful in preventing the spread of HBV. Thus, in 1991, new recommendations were issued for routine vaccination of infants, adolescents, and high risk adults, as well as screening of pregnant women and appropriate preventive care for infants of women who test positive for HBV\textsuperscript{77}. Current recommendations for infants include a birth dose within 7 days or sooner if the mother is HBV positive. After the birth dose infants should receive doses at 2 and 6 to 18 months \textsuperscript{25}. 

1.1.5.4 *Haemophilus influenza* Type B Vaccine

1.1.5.4.1 Epidemiology Overview – *H. influenza* Type B

1.1.5.4.1.1 Organism

Identified as a gram-negative coccobacillus, strains of *Haemophilus influenzae* can be both un-encapsulated and encapsulated. The un-encapsulated strains of *H. influenzae* are non-typable while the encapsulated strains are classified into serotypes A through F, with serotype B being the most pathogenic. Encapsulated strain classification is made based on the composition of the poly-ribitol phosphate polysaccharide. This capsular polysaccharide is responsible for virulence and immunity and each is antigenically and biochemically distinct. *Haemophilus influenzae* grows both aerobically and as a facultative anaerobe but requires accessory growth factors to grow in vitro\(^{29,60}\).

1.1.5.4.1.2 Asymptomatic Colonization

*Haemophilus influenzae* type B (Hib) has been isolated from the nasopharynx of between 0.5% and 3% of otherwise healthy infants but is uncommon in adults\(^{29,90-92}\). Transient colonizations can last for weeks to months and resolve without causing infection. What causes invasion into the bloodstream during the period of colonization is as yet unknown. It is thought that some level of protection is acquired transplacentally from the mother; however, most children have immunity by the age of 6 years\(^{29,60,90}\). Due to low prevalence of asymptomatic nasopharyngeal carriage it is thought that some cross-reactivity occurs to antigenic structures with other naturally colonizing nasopharyngeal bacteria\(^{29}\).
1.1.5.4.1.3 Incidence before and after introduction of *H. influenza* Type B vaccine

Despite not being nationally reportable until 1991, it is estimated that pre-vaccine national incidence was 40 to 50 cases per 100,000 population leading to approximately 20,000 cases annually\(^92\). Following the introduction of Hib vaccine in the 1980s, it is estimated that incidence of Hib has declined over 99\%\(^{90;91;93-95}\). Between 1998 and 2000, an average of only 1,247 cases occurred annually, and only 22\% of these cases were among children under 5 years, the majority of which were serotypes other than type b\(^96\). Among children, the majority of type B cases are un-vaccinated or under-vaccinated children\(^96\).

1.1.5.4.1.4 Risk factors

Risk factors for Hib include crowding, large household size, daycare, low socioeconomic status, low parent education level, and having school-age siblings. Persons of African American, Native American, and Hispanic origin, as well as those with chronic diseases are also at increased risk. Infants who are breastfeeding are at decreased risk of disease\(^90-92\).

1.1.5.4.1.5 Clinical Presentation

*Haemophilus influenzae* type B most often presents as meningitis, however epiglottitis and bacteremia without focus are also common presentations. Other forms of presentation include pneumonia, arthritis, cellulitis, osteomyelitis, and pericarditis. In some cases, onset of infection can include subacute symptoms including low-grade fever for several days and subtle CNS symptoms. In most cases, onset is usually sudden and includes fever, vomiting, lethargy, bulging fontanels in infants and stiff neck and back in older children, and meningeal irritation. Symptoms often progress to stupor or coma\(^29;60\).
The most common presentation of Hib, meningitis, accounted for 50-65% of all pre-vaccine cases. Hib meningitis presents most often with fever, decreased mental status, and stiff neck. Severe sequelae, including hearing impairment, occur in 15% to 30% of cases. Case fatality is between 2% and 5% regardless of appropriate treatment.

Non-typable strains of *Haemophilus influenzae* are a common cause of otitis media. While these strains are less virulent, they can also in some cases cause invasive disease.

1.1.5.4.2 *Haemophilus influenzae Type B Vaccine*

1.1.5.4.2.1 History

The first licensed vaccine against *Haemophilus influenzae* type B was a pure polysaccharide vaccine (HbPV)\(^97\). Licensed in 1985, HbPV was not effective in children under 18 months and effectiveness in children over 18 months varied widely, thus the vaccine was removed from the market in 1988\(^95;98;99\). Since December of 1987, four polysaccharide conjugate vaccines have been licensed in the U.S.: ProHIBIT®, HibTITER®, ActHIB®, and PedvaxHIB®\(^100\). Of these four vaccines, only ActHIB and PedvaxHIB are still in production. The production of PedvaxHIB, produced by Merck, was suspended from late 2007 through early 2010 after a recall of 13 lot numbers due to a suspected problem with product sterility\(^100-103\).

1.1.5.4.2.2 Licensure and Production

ActHIB was licensed to Sanofi Pasteur in 1996 for use in infants. The *Haemophilus b* conjugate vaccine utilizes a tetanus toxoid conjugate and is provided as a
sterile lyophilized powder which is reconstituted with saline diluents for children under one year. The vaccine is created from the *Haemophilus b* capsular polysaccharide from strain 1482 grown on semi-synthetic media and bound to the tetanus toxoid. The tetanus toxoid is created from cultures of Harvard strain *Clostridium tetani* grown in a modified Mueller and Miller medium. The toxoid is extracted, purified with ammonium sulfate, and inactivated using formalin. The toxoid is also filter sterilized prior to conjugation and contains less than 0.5 micrograms of formaldehyde. Reconstitution with a saline diluent creates a 0.5mL dose containing 10 micrograms of capsular polysaccharide conjugated to 24 micrograms of inactivated tetanus toxoid and 8.5% sucrose.

In 1989 Merck & Co., Inc. licensed PedvaxHIB vaccine. This vaccine uses Hib Ross strain covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of *N. meningitides* serogroup B. The bacteria are grown in complex fermentation media and the major virulence factor – polyribosylribitol phosphate (PRP) – is purified through ethanol fractionation, enzyme digestion, phenol extraction, and diafiltration. The OMPC is purified through detergent extraction, ultracentrifugation, diafiltration, and sterile filtration. Each dose contains 7.5 mcg *Haemophilus b* PRP, 125 mcg of *N. meningitides* OMPC and 225 mcg of aluminum hydroxyphosphate sulfate.

In the late 2000s, PedvaxHIB was removed from the market for contamination issues and has only recently resumed production.

### 1.1.5.4.2.3 Efficacy and effectiveness

Studies of ActHib indicated that after the three dose series over 90% of children had antibody levels over 1.0µg/mL. Continuing efficacy trials for ActHIB were terminated due to demonstration of efficacy in the first Hib trial. No cases of Hib were
reported among children who received at least two doses of ActHib[^106]. PedvaxHIB was shown to be effective after just one dose and was 93% to 100% effective after 2 doses[^107]. Receiving doses of different Hib-containing vaccines was also shown to be effective[^108]. In the 1990s, between 30 and 50 vaccine failures were documented each year in the U.S.[^109,110]. One study indicated that among those children under 1 year with vaccine failure, only 9% had evidence of low immunoglobulin levels, thus the reason for vaccine failure is unknown[^109].

### 1.1.5.4.2.4 Safety

Injection site reactions including swelling, redness, and pain, occur in approximately 5% to 30% of vaccine recipients. Fever, irritability, and other systemic reactions are infrequent[^93]. No conditions are specified for injury compensation by the NVICP[^19-21]. The vaccine PedvaxHIB was recalled from the market in December 2007 when routine testing indicated that some microorganisms, particularly *Bacillus cereus*, could have survived the sterilization process; distribution of this vaccine resumed in February of 2010[^100-103].

### 1.1.5.4.2.5 Specific Vaccine Recommendations

For infants starting vaccination between two and six months of age, three doses of ActHIB or two doses of PedvaxHIB should be given at least 2 months apart. If a child is seven to eleven months of age when starting vaccination, then 2 doses of either ActHib or PedvaxHIB should be given two months apart. Vaccination is contraindicated for children with a known allergy to a vaccine component or prior dose, and children under 6
weeks of age. Vaccination should be delayed in children with severe illness but mild to moderate illness is not a contraindication for vaccination 93.

Due to the voluntary recall of PedvaxHIB in 2007, a vaccine shortage was in effect from 2008 through 2009. The CDC, AAFP and AAP recommended deferment of the 15 month booster dose until GlaxoSmithKline was able to increase production102. The PedvaxHIB shortage affected coverage of 19-35 month-old children, and in 2008 the coverage level had decreased almost 2% from the 2007 levels 102;111.

1.1.5.5 Pneumococcal Conjugate Vaccine

1.1.5.5.1 Epidemiology Overview – Pneumococcal Disease

1.1.5.5.1.1 Organism

Pneumococcal disease is caused by the bacterium Streptococcus pneumoniae, a gram-positive, encapsulated, diplococcic, for which over 90 capsular serotypes have been described. The capsular polysaccharides are responsible for the pathogenicity and the type-specific antibody production that provides immunity to individual serotypes 29. The 10 most frequent serotypes are estimated to account for 62% of disease worldwide; however, the prevalence of a single serotype varies by age, ethnicity, and geographic region 112;113.

1.1.5.5.1.2 Asymptomatic Colonization

Asymptomatic nasopharyngeal colonization with S. pneumoniae is common and occurs in approximately 5% to 70% of healthy adults, varying with age, environment, and geographical region 29. Approximately 21%-59% of children are colonized with S. pneumoniae. Risk factors for increased nasopharyngeal colonization include crowding
and spending time with children. \textit{S. pneumoniae} can usually be cultured from nasopharyngeal swabs of colonized adults for two to four weeks but can persist as long as six months without causing infection. The immunologic mechanism that allows disease to occur in a carrier of \textit{S. pneumoniae} is not understood\textsuperscript{29,60,114}.

1.1.5.5.1.3 Incidence of Pneumococcal Disease Before and After Introduction of Pneumococcal Conjugate Vaccine

In 1998, before the introduction of the pneumococcal conjugate vaccine, it was estimated that invasive pneumococcal disease (IPD) incidence was approximately 24 cases per 100,000 population. Incidence was higher for children under two years (188 cases per 100,000 population) and adults over 65 years (61 cases per 100,000 population)\textsuperscript{114}. The CDC estimated that in 1998 150,000-570,000 cases of pneumococcal pneumonia occurred in the U.S. with the greatest incidence among persons over 65 years\textsuperscript{114-116}. Prior to the introduction of the pneumococcal conjugate vaccine (PCV), \textit{S. pneumoniae} was attributed with over 5 million cases of otitis media in children annually\textsuperscript{114}.

By 2001, the seven-valent pneumococcal conjugate vaccine (PCV-7) was associated with a 97\% decline in the incidence of vaccine related pneumococcal disease\textsuperscript{117}. All cause pneumococcal disease was reduced by 89\% regardless of whether or not the serotype was contained within the vaccine\textsuperscript{117}. It was also estimated that there was a 7\% reduction in acute otitis media among children receiving PCV-7\textsuperscript{117}. However, by 2004 it became evident that serotype replacement was occurring. While incidence of pneumococcal disease remained 76\% lower than the pre-vaccine era, significant increases were seen for non-vaccine serotypes, particularly 19A\textsuperscript{118,119}. In children younger than 5 years, the proportion of pneumococcal disease related to 19A increased from 8\% pre-
vaccine to 26% in 2001-2003, and a surprisingly large proportion of these isolates exhibited some antibiotic resistance\textsuperscript{118;120}. The increased incidence and antibiotic resistance due to serotype replacement prompted the development and licensure of the 13-valent pneumococcal conjugate vaccine (PCV-13)\textsuperscript{121}.

Pre-licensure data for PCV-13 indicated that approximately 64% of pneumococcal disease in children younger 5 years was caused by the additional six serotypes in PCV-13 \textsuperscript{113;121}. Predictive modeling of the public health impact of PCV-13 indicated that over 10 years use of PCV-13 instead of PCV-7 would reduce the incidence of IPD by 106,000, all-cause hospitalized pneumonia by 948,000, and non-hospitalized pneumonia by 1.93 million cases\textsuperscript{122}. Further, the incidence of pediatric acute otitis media would be reduced by 16.3 million cases\textsuperscript{122}. Early reports indicate that the incidence of IPD among children under two years was reduced by 50% in the first year of PCV-13 use\textsuperscript{123}. This is supported by studies indicating that nasopharyngeal carriage of \textit{S. pneumoniae} serotypes not contained in PCV-7 was reduced from 64.6% to 53.9% in children receiving PCV-13 compared to those receiving PCV-7\textsuperscript{123}.

1.1.5.5.1.4 Risk factors for Disease

Pneumococcal infections have a temporal trend and are more common during the winter and early spring similar to other upper respiratory infections. Invasive pneumococcal disease most commonly occurs in young children under 6 years of age and adults over 65 years of age. Children and adults with underlying medical conditions are also at increased risk. Conditions known to increase the risk of IPD include decreased immune function, functional or anatomic asplenia, chronic heart disease, pulmonary
disease including asthma, liver disease, renal disease, smoking, cochlear implant, and cerebrospinal fluid (CSF) leak. 

1.1.5.5.1.5 Clinical Presentation

Pneumococcal disease presents as pneumonia, bacteremia, or meningitis, the latter two presentations are considered IPD. *S. pneumoniae* is also associated with non-invasive disease including otitis media, sinus infections, and mastoiditis.

In pneumococcal pneumonia, symptoms occur rapidly and include fever, pleuritic chest pain, cough productive of mucopurulent, rusty sputum, shortness of breath, rapid breathing, poor oxygenation, rapid heart rate, malaise, and weakness. Headache, nausea, vomiting, and chills with rigors occur less frequently. While meningitis associated with *S. pneumoniae* can occur without a known focus, pneumococcal meningitis can be a complication associated with acute otitis media and mastoiditis. Diagnosis is usually made via isolation of pneumococcal capsular polysaccharide from blood or CSF fluid. Symptoms of pneumococcal bacteremia include fever, chills, malaise, headache, muscular aches and pains, rapid heart rate, and rapid breathing.

1.1.5.5.2 Pneumococcal Conjugate Vaccines

1.1.5.5.2.1 History

While a pneumococcal polysaccharide vaccine has been in production since 1977, it is only recommended for children over 2 years who have normal immune systems and an underlying illness such as cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis, cerebrospinal fluid leaks, or a cochlear implant. The PCV-7 in
and now the PCV-13 licensed in 2010 are commonly used among children under six.

1.1.5.5.2.2 Licensure and Production

The PCV-7, produced by Wyeth Lederle Vaccines, was licensed in February 2000 for use in children age 2 months to 59 months. The vaccine contained seven purified capsular polysaccharides of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, and 23F) and was potentially cross-reactive with an additional five serotypes (6A, 9A, 9L, 18B, and 18F). The vaccine includes purified capsular polysaccharides for the 7 serotypes conjugated with a nontoxic variant of diphtheria toxin (CRM197). Each 0.5mL dose of the vaccine includes 20mcg of capsular polysaccharide, 20mcg of CRM197, and 0.125mg of aluminum phosphate adjuvant. These twelve serotypes accounted for 86% of bacteremias, 83% of meningitis cases, and 65% of acute otitis media cases between 1978 and 1994 among children under six years of age in the U.S.

The PCV-13 vaccine, produced by Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc., was licensed in February of 2010 and replaced PCV-7; it covers the original serotypes in PCV-7 with the addition of serotypes 1, 3, 5, 6A, 7F, and 19A. The vaccine contains polysaccharides from the capsules of the 13 *S. pneumoniae* serotypes conjugated to a nontoxic diphtheria cross-reactive material (CRM) carrier protein. The vaccine itself contains 28mcg of capsular polysaccharides, 34mcg of CRM, and 0.125mg of aluminum phosphate adjuvant.
1.1.5.5.2.3 Efficacy and effectiveness

Trials were conducted to determine the efficacy of PCV-7 in preventing IPD. The efficacy among fully vaccinated children was 97.4% (95% CI = 82.7% - 99.9%) and among partially vaccinated children the efficacy was 93.9% (95% CI = 79.6% - 98.5%)\textsuperscript{127}. For each individual serotype there was a statistically significant serotype-specific protection for 19F, 14, 18C and 23F but not enough cases were identified through surveillance to evaluate serotypes 4, 9V, and 18C\textsuperscript{127}.

The effectiveness of PCV-7 to prevent other diseases associated with \textit{S. pneumoniae} was assessed. Among children with at least 1 dose of PCV-7 there was an 11.4% decrease in the number of episodes of clinical pneumonia\textsuperscript{127}. The PCV-7 vaccine was also associated with a 6.4% reduction in episodes of acute otitis media\textsuperscript{127}.

Immunogenicity clinical trials indicated that replacing PCV-7 with PCV-13 in the primary series induced sufficient antibody response for the 6 additional serotypes and comparable antibody response for the 7 serotypes in PCV-7\textsuperscript{121}. The schedule of 3 doses of PCV-7 with 1 dose of PCV-13 was compared to 4 doses of PCV-13 showing that the single additional dose was able to provide adequate protection against the six additional serotypes\textsuperscript{121}. Effectiveness trials for PCV-13 are not yet available.

1.1.5.5.2.4 Safety

In general 10% to 20% of PCV-7 recipients had local reactions (e.g., pain, swelling, or erythema); however, only 3% of these reactions were considered severe (e.g., tenderness interfering with limb movements)\textsuperscript{127-129}. Fever over 100.4°F within 48 hours of receiving PCV-7 was reported among children approximately 15% to 24% of the time\textsuperscript{127-129}. Studies suggest that receiving the diphtheria, tetanus, and acellular pertussis
vaccine at the same visit increases the likelihood of fever among children\textsuperscript{121,125}. While some severe complications, including death, occurred during the clinical trials, none were associated with receipt of PCV-7 vaccine \textsuperscript{125}. Contraindications for PCV-7 include hypersensitivity to known components of the vaccine. Physicians may want to delay receipt of vaccine for children with moderate to severe illness, however respiratory illnesses with or without low grade fever are not a contraindication for vaccination\textsuperscript{121}.

Initial studies on safety indicated that the safety profile for PCV-13 was similar to that of PCV-7. Over 20\% of children experienced side effects including pain, swelling, fever, decreased appetite, irritability, and increased or decreased sleep. Severe systemic reactions were not reported\textsuperscript{121,125}.

While the NVICP lists no illness, disability, injury, or condition covered for pneumococcal conjugate vaccines, the program has received a total of 34 filed claims related to the PCV-7 and PCV-13 vaccines, 30 injuries and 4 related deaths. Seven of these claims have been compensated to date\textsuperscript{19,20} (Appendix 1, Table 1). In general, the PCVs they have been shown to be generally safe and effective over the 11 years of experience with administration. It remains to be seen if further serotype replacement will occur with the introduction of PCV-13.

\textbf{1.1.5.5.2.5 Specific Vaccine Recommendations}

Pneumococcal conjugate vaccine is recommended for children at 2, 4, 6, and 12-15 months. Children receiving their first dose of PCV at 7 months or older should receive 2 doses spaced 2 months apart and a third dose between 12 and 15 months. Children receiving their first dose of PCV after 12 months should receive only 2 doses spaced 2 months apart. Children receiving their first dose after 24 months should only receive a
single dose, unless they are high risk and then a second dose should be given at least 2 months after the first dose.\textsuperscript{115;130;131}

With the licensure of PCV-13, ACIP recommended that PCV-13 replace PCV-7 in the recommended vaccination schedule for children under 6 years. They also recommended a “catch-up” period where children age 12 to 59 months who had previously completed the PCV-7 series should receive a single supplemental dose of PCV-13 to expand their coverage. Pneumococcal conjugate vaccine is licensed for children age 2 months to 59 months and should not be given before 6 weeks of age.\textsuperscript{121}

1.1.5.6 Rotavirus Vaccine

1.1.5.6.1 Epidemiology Overview – Rotavirus Gastroenteritis

1.1.5.6.1.1 Organism

Rotoviral enteritis is caused by the rotavirus, a 70-nanometer double-stranded RNA virus from the Retroviridae family. Rotavirus has six groups labeled A, B, C, D, E, and F of which, only A, B, and C are known to cause infections in humans. Group A is the most common while Group B is less common in infants but known to cause large outbreaks in countries such as China, and Group C is the least common in humans. Each group has both major and minor serotypes based on the antigenic differences among the viral protein 7 (VP7) outer capsid surface protein, often referred to as G protein when delineating strains of rotavirus. Virulence is often determined by the viral protein 4 (VP4), often referred to as P protein when classifying strains of rotavirus. The virus composed of three concentric shells encoded on 11 gene segments is incredibly stable and remains viable in the environment for weeks to months if not disinfected.\textsuperscript{29;60} In the
U.S., during the decade from 1996-2005, Group A serotypes G1-4 and G9 accounted for 90% of rotaviral enteritis among children younger than 5 years, more than 75% of which were attributed to a single serotype G1 132.

1.1.5.6.1.2 Pathogenesis

After entering the body via the mouth, rotavirus replicates in the villus epithelium of the proximal small intestine. Infection with rotavirus destroys the epithelial surface leading to isotonic diarrhea 133;134. The destruction of the epithelial surface allows for increased shedding of rotavirus in large quantities, although only a small number of virions are needed to cause infection thus increasing communicability within families, institutions, hospitals and child care settings 133;134. Viral replication outside of the intestine leading to viremia is uncommon 29.

1.1.5.6.1.3 Incidence before and after introduction of Rotavirus vaccine

Prior to the introduction of the RV5 vaccine (Rotateq) in 2006 it was thought that at least 95% of all children were infected at least once by age 5 years with the highest incidence being among children age 4 months to 35 months 134-136. Annual estimates in the pre-vaccine era indicated that almost 3 million cases of rotaviral enteritis occurred in the U.S., mostly between November and May 137. In the U.S. specifically, rotavirus peaks earliest in the southwest toward the beginning of winter (November-December) and moves east peaking in the northeast in early spring (April-May) 29.

While pre-vaccine rotavirus accounted for 5% to 10% of all gastroenteritis episodes among children younger than 5 years (Rodriguez 1987), rotavirus accounted for 30%-50% of hospitalized episodes among this age group 137. In the pre-vaccine era it was
estimated that rotavirus was responsible for 400,000 physician visits, 200,000 emergency department visits, 55,000 to 70,000 hospitalizations, and 20-60 deaths annually.\(^{138}\)

Estimating incidence in the post-vaccine era is complicated by the fact that rotaviral enteritis is not a reportable condition. However, analysis based on data from the National Respiratory and Enteric Viruses Surveillance System (NREVSS) indicated that when compared to the pre-vaccine era of 2000-2006 the number of positive rotaviral tests decreased by 64% for the 2007-2008 season and 59% for the 2008-2009 season. Other studies have also documented a decline in rotavirus hospitalizations and office visits.\(^{29,60,139-142}\) A study by Payne, et al. (2011) indicated that compared with the 2006 hospitalizations, the number of admissions in 2008 were reduced by 87% in 6- to 11-month-olds, 96% in 12- to 23-month-olds, and 92% in 24- to 35-month-olds among the study population.\(^{143}\) Other studies indicate rotavirus is responsible for between 27 and 39 hospitalizations per 10,000 children under 5 years of age in the post-vaccine era.\(^{144,145}\)

### 1.1.5.6.1.4 Risk factors

Given the pervasiveness of the virus, almost all children are at risk for rotaviral enteritis. However, certain groups, including children attending daycare and children in hospital wards, as well as their caretakers, are at increased risk.\(^{138}\) Immunocompromised children and adults are also at increased risk of rotaviral enteritis, particularly for severe complications.\(^{146-148}\) Increased risk for hospitalization due to rotaviral enteritis includes: male gender, lack of breastfeeding, low birth weight, siblings under 24 months, low socioeconomic status, and day care attendance.\(^{149,150}\)
1.1.5.6.1.5 Clinical Presentation

Cases of rotaviral enteritis range from mild to severe. Illness usually presents 24 to 48 hrs after exposure and begins with acute onset of fever, often over 102°F in children, and vomiting lasting less than 24 hours. Diarrhea usually begins 24 to 48 hours after onset of fever and vomiting and can last generally from 3 to 7 days. Severe rotaviral enteritis, often resulting in hospitalization, is associated with increased vomiting, diarrhea, and fever which can result in dehydration with shock, electrolyte imbalance, and in some cases death. Adult infections are often less severe than childhood infections and result in either asymptomatic infection or a shorter duration of symptoms\(^{29,60}\).

1.1.5.6.2 Rotavirus Vaccine

1.1.5.6.2.1 History

Rotavirus vaccine first became available on the U.S. market in 1998 with the licensure of RotaShield by Wyeth (now owned by Pfizer, Inc.)\(^{151;152}\). Intussusception, a severe bowel obstruction, was reported in approximately one in 10,000 vaccinated children, thus prompting the company to withdraw the vaccine\(^ {153}\). Two oral rotavirus vaccines are available today: Rotarix and RotaTeq\(^ {138}\).

1.1.5.6.2.2 Licensure and Production

The RotaTeq (RV5) live oral vaccine was licensed in February of 2006 to Merck & Co., Inc., and contains \(2 \times 10^6\) infectious units each of five reassortant rotaviruses. The reassortant rotaviruses were developed from Bovine strain Wistar Calf 3 (WC3) and each strain expresses one of the outer capsid proteins (G1-G4 and G6). The first four reassortant rotaviruses also express attachment protein P7 while the fifth strain expresses
attachment protein P1A. To create the reassortant strains, the WC3 rotavirus was passed 12 times in African green monkey kidney cells and the strains were then propagated in the absence of antifungal agents by using standard tissue culture techniques and Vero cells\textsuperscript{154}. Clinical trials showed a seroconversion rate, defined as a threefold increase in IgA antibodies, to be between 93\% and 100\% \textsuperscript{154}. Antibody response is not reduced when administered with other recommended vaccines including Hib, IPV, HepB, PCV, and DTaP\textsuperscript{143;155;156}.

The monovalent human rotavirus vaccine (Rotarix or RV1) was licensed to GlaxoSmithKline in April 2008. The live oral vaccine was created from a human strain isolated in 1988; the virus was passaged 33 times in African green monkey kidney cells and then further attenuated by cloning and passaging in a Vero cell line \textsuperscript{157}. The attenuated strain is called RIX 4414 and exhibits outer capsid protein G1 and attachment protein P1A. Unlike RV5, which comes premixed, RV1 is licensed as a lyophilized powder which must be reconstituted with a calcium bicarbonate buffer; each 2mL reconstituted dose contains \(10^6\) infectious particles \textsuperscript{157}. Seroconversion, defined as at least 20U/ml of antirotavirus IgA antibodies, occurred in 76\% to 86\% of infants \textsuperscript{157}. No decrease in immunogenicity was seen when administered in conjunction with other recommended vaccines \textsuperscript{157}.

\textbf{1.1.5.6.2.3 Efficacy and effectiveness}

The phase III efficacy and safety trials among children in both the U.S. and Finland, following children for one season post completed vaccination, suggest that the efficacy of RV5 against G1-G4 rotaviral enteritis is 74\% and increases to 98\% for severe rotaviral enteritis \textsuperscript{158}. Healthcare utilization for rotaviral enteritis was reduced 86\% for
office visits, 93% for emergency room visits, and 95% for hospitalization. The efficacy of RV5 does not seem to be affected by breastfeeding or preterm status. Fecal shedding of rotavirus vaccine was seen in 12% of infants 1 to 15 days after administration but not in infants receiving dose 2 or 3, suggesting no transmission of vaccine strain rotavirus although transmission was not assessed.

The efficacy of RV1 was assessed in Latin America and Europe. In Latin America, the efficacy against all rotaviral gastroenteritis was 40% and against severe rotaviral gastroenteritis was between 80% and 84%. In Europe, efficacy of RV1 during the first season after vaccine series completion was 87% for all rotaviral gastroenteritis and 95% for severe rotaviral gastroenteritis. The efficacy dropped slightly in the 2nd season to 78% for all rotaviral gastroenteritis and 90% for severe rotaviral gastroenteritis. The efficacy of the two-dose series against hospitalization was 74%. Efficacy was not affected by breastfeeding. Shedding of vaccine strain virus was seen for up to 60 days after dose 1 and 30 days after dose 2, however, transmission of vaccine strain virus to other individuals was not assessed.

While rotavirus is not a reportable disease and effectiveness studies are ongoing, the National Respiratory and Enteric Virus Surveillance System (NREVSS) and the New Vaccine Surveillance Network (NVSN) capture cases of rotaviral enteritis. Data from these surveillance networks suggest that the 2007-08 rotavirus season was delayed by 2-4 months compared to the previous 15 rotaviral seasons. The NVSN indicates that the proportion of positive specimens compared to all submitted for rotavirus was 51% in 2006, 54% in 2007, and only 6% in 2008 suggesting vaccine effectiveness.
1.1.5.6.2.4 Safety

Children receiving RV5 had a statistically higher incidence of vomiting, diarrhea, otitis media, nasopharyngitis, and broncospasm in the first 42 days after vaccination 154. In clinical trials, both the RV5 and placebo groups had similar incidences of fever, hematochezia, gastroenteritis, pneumonia, and death 154;162. The safety study designed to assess intussusception among children found that the risk of intussusception was 1.6 (95% CI = 0.4-6.4) indicating no increased risk 154. The safety profile for the vaccine is also similar for preterm infants 159. Post-licensure monitoring of VAERS and VSD for RV5 indicated reports of but no increased risk for intussusception, hematochezia, Kawasaki syndrome, seizures, meningitis/encephalitis, myocarditis, and gram-negative sepsis 163.

Safety of RV1 was assessed in several clinical trials; overall no differences were seen between vaccine and placebo groups for pneumonia, death (although one study did have a higher rate of pneumonia-related deaths among the RV1 group), fever, fussiness/irritability, loss of appetite, and vomiting 156;157;160. However, a few studies found increases in diarrhea, dehydration, gastroenteritis, and cough/runny nose 156;157. None of the studies found differences for intussusception 156;157;160.

Contraindications exist for vaccine administration including children who have a history of anaphylaxis to a previous dose of rotavirus, or latex rubber, although RV5 is latex-free 138. Children experiencing acute gastroenteritis should not be vaccinated until the episode has passed, although mild gastroenteritis is not a contraindication for vaccination 138. There are several listed precautions for conditions potentially exacerbated by rotaviral vaccination; however, safety information does not exist for many
of these conditions and the ACIP recommendations indicate that children with these conditions could benefit from vaccination. These conditions include altered immunocompetence (congenitally or from HIV)\textsuperscript{138}, chronic gastrointestinal disease, spina bifida and bladder extrophy. While there is no indication that RV5 or RV1 increase the risk of intussusception, practitioners are advised to consider the increased risk of repeat episodes in children with a history of intussusception. Preterm delivery, exposure to immunocompromised persons, and exposure to pregnant women are not contraindications for vaccination according to the normal vaccine schedule\textsuperscript{138}.

Between October 1, 1988 and July 2, 2012, there were 53 claims filed with the National Childhood Vaccine Injury Act despite no listed illness, disability, injury or conditions eligible for coverage. Of these claims, 28 were compensated. It should be noted that these claims include the previously removed RotaShield vaccine\textsuperscript{19,20} (Appendix 1, Table 1).

\subsection*{1.1.5.6.2.5 Specific Rotavirus Vaccine Recommendations}

The ACIP recommendations do not express a preference for either RV5 or RV1, except in cases with latex allergy\textsuperscript{25}. These two vaccines differ in composition and schedule of administration, however, neither vaccine contains preservatives or thimerosal. The RV5 is administered in a three-dose series at 2, 4, and 5 months. The RV1 is administered in a two-dose series at 2 and 4 months. The minimum age for dose one is 6 weeks and neither series should begin after 14 weeks and 6 days. The minimum interval between doses is 4 weeks. While there is no maximum interval between doses listed, no doses should be administered after 8 months 0 days. Administration of the vaccine series should continue despite rotaviral gastroenteritis infection and no feeding
restrictions are listed\textsuperscript{138}. While ACIP recommendations state that it is preferable to start and complete the series with the same formulation, switching formulations is not prohibited. This vaccine can be administered simultaneously with all other recommended vaccines for this age group, however, use of other live oral vaccines such as OPV or nasal influenza have not been studied\textsuperscript{138}.

1.1.5.7 Combination Vaccines

1.1.5.7.1 Pediarix

Pediarix\textsuperscript{®} was licensed by the FDA in 2002 to GlaxoSmithKline and covers DTaP, IPV, and HepB vaccines\textsuperscript{59}. Each dose contains 25Lf of diphtheria toxoid, 10Lf of tetanus toxoid, 25mcg of inactivated pertussis toxin, 25mcg of filamentous hemagglutinin, 8mcg of pertactin, 10mcg of HBsAg, 20 D-antigen Units (DU) of Type 1 poliovirus, 8 DU of Type 2 poliovirus, and 32 DU of Type 3 poliovirus\textsuperscript{59}. Clinical trials showed that Pediarix produced an immune response and effectiveness that was not inferior to separate injections of HepB, DTaP, and IPV. Injection site reactions, fever, drowsiness irritability, and loss of appetite occurred in over 25\% of children receiving Pediarix. During clinical trials, children who received Pediarix had a higher incidence of fever compared to children who received the components separately; however, post-marketing safety surveillance did not indicate the same increased risk\textsuperscript{59,164-166}.

1.1.5.7.2 Pentacel

Pentacel\textsuperscript{®} was licensed to Sanofi Pasteur in June of 2008 and contains the vaccines DTaP, IPV and Hib\textsuperscript{167}. Each dose of Pentacel contains 15Lf diphtheria toxoid, 5Lf tetanus toxoid, 20mcg pertussis toxin, 20mcg filamentous hemagglutinin, 3mcg pertactin, 5mcg fimbriae types 2 and 3, 40 DU Type 1 poliovirus, 8 DU type 2 Poliovirus,
32 DU Type 3 poliovirus, 10mcg PRP of *H. influenzae* type b covalently bound to 24mcg of tetanus toxoid, 1.5mg aluminum phosphate, polysorbate 80, 42.5mg sucrose, 5mcg formaldehyde, 50ng glutaraldehyde, 50ng bovine serum albumin, 3.3mg 2-phenoxyethanol, and 4pg neomycin and polymyxin b sulfate \(^{167;168}\).

Overall, Pentacel was considered effective against all diseases targeted by components of the vaccine. The efficacy of Pentacel was comparable for diphtheria, tetanus toxoid, and poliovirus. However, studies showed a slightly lower immune response to the pertussis component anti-pertactin compared to Daptacel and mixed immunogenicity results for Hib compared to ActHib. It is unclear how these results will affect effectiveness against pertussis and Hib \(^{167-170}\).

The number of adverse events associated with Pentacel varies by dose, but in general about 50% of children receiving Pentacel are irritable and cry following injection. Approximately 30% of children have injection site redness, pain, and swelling. Overall safety was comparable to the individual administration of these vaccines \(^{167-170}\).

1.1.5.7.3 Comvax

Comvax® was licensed to Merck & Co., Inc. in October of 1996 for vaccination against Hib and HepB \(^{171}\). Each dose of Comvax has 7.5mcg PRP conjugated to 125mcg OMPC, 5mcg HBsAg, 225mcg aluminum, and 35mcg sodium borate \(^{83;171}\). The efficacy of Comvax for Hib is comparable to that of administration of each component separately but simultaneously, and higher than just Hib alone \(^{83;171;172}\). The efficacy of Comvax for HepB is statistically lower than co-administration of each component (separately but simultaneously). The safety of Comvax is equivalent to administration of its components separately. The largest number of children, approximately 50% for doses 1 and 2,
experienced irritability or drowsiness. Comvax has been found safe when administered concomitantly with other vaccines recommended at the 2, 4, and 6 month well child visits.

1.1.5.7.4 Recommendations on the use of combination vaccines

The ACIP recommendations concerning the use of combination vaccines is as follows: “Licensed combination vaccines can be used whenever any components of the combination are indicated and its other components are not contraindicated and if licensed by the FDA for that dose in the series.” There are many advantages and disadvantages of combination vaccines. Advantages include fewer injections for recommended vaccines and reduced costs for purchase, shipping, storage, and integration of vaccines as well as increased vaccine coverage. Disadvantages include the potential for increased adverse events, reduced immunogenicity to some components, increased confusion over vaccine selection, and administration of extra doses of some vaccine components. A study of children in Washington State indicated that Pentacel use can be as high as 50%, thus care should be exercised by physicians when choosing which combination vaccines to use and when they are administered.

1.1.6 Current Vaccine Coverage in the U.S.

The use of vaccines among the U.S. population has never been 100%. The U.S. tracks childhood immunization coverage for children age 19 - 35 months through the National Immunization Survey (NIS). By 19 months of age, children should have completed their primary series of vaccines having received at least one dose of 11 recommended vaccines protecting against 14 diseases.
Individual vaccine coverage was above 90% for several recommended vaccines in 2011 including: at least 1 dose of MMR (91.6%) and varicella (90.8%) and at least three doses of HepB (91.1%) and IPV (93.9%) 176. Coverage was lowest for the newest recommended vaccines: rotavirus (67.3%), four doses of PCV (84.4%), and HepA (81.2%) 176 (Appendix 1, Table 3).

Coverage for individual vaccines (e.g. PCV, Poliovaccine, Hib, etc.) is higher than the current 4:3:1:3:3:1:4 vaccine series. The 4:3:1:3:3:1:4 vaccines series is often used as a benchmark for full vaccine coverage and includes: ≥ 4 doses of DTaP/DT/DTP, ≥ 3 doses of poliovirus vaccine, ≥ 1 dose of measles-containing vaccine, full series of Hib vaccine (3 or 4 does depending on product type), ≥ 3 doses of HepB, ≥ 1 dose of varicella vaccine, and ≥ 4 doses of PCV 25;176. In 2011, coverage of the 4:3:1:3:3:1:4 vaccine series among children aged 19 to 35 months was 68.5% 176. From December of 2007 through June of 2009 a recall of Hib vaccine due to safety reasons caused a national shortage of Hib 102;111;177. Due to the shortage, it was thought low coverage of the 4:3:1:3:3:1:4 vaccine series may be due to under-immunization with Hib vaccine. However, coverage in 2011 for the series without Hib (4:3:1:-:3:1:4) was only slightly higher at 73.6% 176.

Coverage in New York State (NYS), outside New York City (NYC) for the 4:3:1:-:3:1:4 vaccine series among children age 19 to 35 months in 2011 was 63.7% which is below national estimates 176. Among the same population, estimated coverage for NYS, outside NYC, for ≥ 4 doses of DTaP was 82.0% and for Rotavirus was 60.9% in 2011, other vaccines given among children under one year are not reported by NIS by state 176 (Appendix 1, Table 5).
1.1.7 Socio-demographic Factors Affecting Vaccine Coverage

Studies examining factors affecting vaccination coverage often separate children into two groups, under-vaccinated children and unvaccinated children 100;116-119. Children are considered to be up-to-date (UTD) for a vaccine if they have received all age appropriate doses of that vaccine (e.g. a 9 month old child is UTD for DTaP if they have received 3 doses) 25. Children who have not received all age appropriate recommended doses of a vaccine are considered to be under-vaccinated. If a child receives no age appropriate doses of a vaccine they are considered to be un-vaccinated. While some unvaccinated children receive no vaccine others selectively receive only some vaccines. Similarly, under-vaccinated children can be up-to-date for some vaccines and not for others. Children who are under-vaccinated have significantly different socio-demographic characteristics from unvaccinated children 178-180.

The NIS estimates that, nationally, less than 1% of children ages 19 to 35 months are un-vaccinated 176. Unvaccinated children are often born to parents of specific religious groups, including Catholic, Christian Scientist, or Amish, have higher socio-economic standing and may be demographically confined to specific areas 178;180-184. Parents who are against vaccination often have similar ideologies, including a perceived low risk and/or severity of disease, and high mistrust of vaccines 178. Persons of an anti-vaccination mindset also tend to cluster in specific geographic areas, reflecting the importance of the community in shaping and maintaining perceptions 182;183.

Risk factors for under-vaccination include low education level of parents, large family size, low socioeconomic status, non-white race, Hispanic ethnicity, young parental age, lack of prenatal care, lack of health insurance, demographic region and use of public
clinics. The NIS survey in 2011 indicates that under-vaccination is associated with low socioeconomic status despite the introduction of programs, such as VFC which provides no-cost vaccine to children who are Medicaid eligible, uninsured, or underinsured. National immunization coverage for the 4:3:1:3:1:4 vaccine series is statistically lower among impoverished children. Crude coverage estimates show that coverage with the 4:2:1:3:1:4-vaccine series is lower among black children but this association is primarily due to confounding by poverty status (Appendix 1, Table 4).

The association between under-vaccination, defined as not being UTD at an age-related milestone, and access to healthcare has been widely studied. In 2005, Lumen, et al., found that the most common period for children to fall behind was 16 to 19 months during which time only 49% of children had a vaccine-eligible visit in comparison with other periods where more than 80% of children had a vaccine eligible visit. However, the theory that missed visits account for under-vaccination has been challenged by studies which show that 60% of infants who are not UTD at 8 months had at least 3 well-child-visits. Robison, et al., found the percentage of not-UTD children due to lack of health care access ranged from 5.5% at 3 months to a high of 19.8% at 19 months, whereas, children who had a health care visit where vaccines were not administered ranged from 12.1% at the 3 month milestone to a high of 30% at the 7 month milestone. This data illustrates that physicians also miss opportunities to vaccinate and this, in turn, affects vaccination coverage.

1.1.8 Physician Factors Affecting Vaccination

Provider recommendation for vaccination is one of the strongest factors for increasing vaccination coverage. Most reports indicate providers have positive
attitudes toward vaccination and their role in vaccination. However, physicians, like parents, are susceptible to concerns regarding vaccine-associated adverse events. A pediatric survey in 2000 indicated that four percent of pediatricians refused immunizations for their own children. Providers base their fears on reported safety problems such as when the MMRV vaccine was strongly associated with increased febrile seizure or rotavirus vaccine which had previously been associated with intussusception, both vaccines are no longer available today. The under-vaccination of children may be associated with some physicians’ lack of knowledge regarding contraindications to vaccination.

Failure to administer all qualified doses of vaccine at a health care visit either through a records error, inappropriately perceived contraindications, or vaccine supply shortages is often referred to as a missed vaccination opportunity. A survey of physicians indicated that one third of physicians had difficulty catching children up when they fall behind on immunizations. These missed opportunities lead to delays in vaccine administration which are significantly associated with UTD status.

Record fragmentation and the increasing complexity of the childhood vaccine schedule, which has increased by at least seven injections since 1999, is associated with physicians failing to administer all recommended vaccines during an office visit. Many physicians also do not realize that unconventional settings, such as a sick-care visit or the emergency room are also opportunities to vaccinate children. Providers often do not immunize outside of a well-child visit for one of two reasons, first the mistaken belief that vaccination is contraindicated when a child is at an acute care visit, and second, that needing vaccines encourages parents to make well-child visits. While
contraindicated during some acute illnesses, illness is not necessarily a contraindication to vaccination\textsuperscript{25}.

Some physicians also express discomfort with the growing number of injections at each well-child visit\textsuperscript{194;195;204}. Madlon-Kay and Harper found 74\% of nurses were uncomfortable giving more than three injections at one visit\textsuperscript{194}. Pielak, et al., found that nurses are less likely to have negative attitudes about multiple injections, and feel pressured to administer all recommended doses at a given visit\textsuperscript{195}.

1.1.9 Parental Factors Associated with Vaccination

Under-vaccination is associated with a longer wait time at the doctor’s office, having to take time off from work for an appointment, and the belief that vaccine timing is unimportant\textsuperscript{185;205;206}. Parents also often perceive their children as being UTD when they are not due to the complexity of the current vaccination schedules\textsuperscript{185;186;206;207}.

Under-vaccination may also be associated with parental misconceptions regarding vaccination. In 2000, Gellen, et al., found that between 19\% and 25\% of parents have misconceptions about vaccination\textsuperscript{206}. Misconceptions included believing multiple immunizations at one time could weaken a child’s immune system, vaccines could cause disease, and that children got more immunizations than are good for them\textsuperscript{206}. The influence of parental perception on children being under-vaccinated also seems to be associated a parent’s discomfort with the pain the child experiences during a vaccination health care visit. Some studies have shown that parents become more resistant to vaccination as the number of injections per visit increases\textsuperscript{190;194;204;206}, however, the use of combination vaccines and physician counseling can overcome these fears\textsuperscript{194;208}.
Monitoring parents’ attitudes towards vaccination is an important part of maintaining and improving vaccination coverage in the U.S. Chen et al. documented that as vaccine programs become more successful and incidence of disease is significantly lowered, parents become more aware of and concerned about potential vaccination side effects \(^{209}\) (Appendix 4). Prominent media attention surrounding vaccine safety has increased parental concern regarding the safety and efficacy of vaccines \(^{188-190,207,210-213}\). Despite increased media coverage and awareness of anti-vaccine campaigns, the number of non-vaccinated children remains low, yet as many as 1 in 10 parents may be altering their child’s vaccination schedule intentionally due to fear of adverse events \(^{214,215}\).

1.2 The Anti-Vaccine Movement – A Brief Overview

1.2.1 History of the Anti-Vaccine Movement in the United States

Individuals have opposed the use of vaccines as long as the practice of vaccination has existed. However, the modern anti-vaccine movement, as one would recognize it today, formed in response to mandatory smallpox vaccination laws in early 19\(^{th}\) century England \(^{216,217}\). Implementation of similar smallpox vaccination laws in the U.S. prompted the importation of the anti-vaccine movement to the U.S. by a British anti-vaccinationist, William Teb, who helped found the Anti-Vaccination Society of America in 1879 \(^{218,219}\). Shortly thereafter, the New England Anti Compulsory Vaccination League was founded in 1882 and the Anti-vaccination League of New York City was founded in 1885 \(^{219}\).

Fighting to uphold the American ideal of individualism and blaming general filth for the spread of smallpox, anti-vaccination groups were able to repeal smallpox
vaccination laws in California, Illinois, Indiana, Minnesota, Utah, West Virginia, and Wisconsin. At the turn of the 20th century, vaccination coverage was low and a reemergence of smallpox lead to the institution of compulsory smallpox vaccination laws. In 1905, the now landmark ruling of the U.S. Supreme Court in *Jacobson vs. Massachusetts*, upheld the right of states to implement public health laws concerning compulsory vaccination.

Despite the success of smallpox vaccinations in reducing and subsequently eliminating smallpox, anti-vaccine sentiment increased in the 1920s as states began implementing mandatory vaccinations for acceptance into public schools. In the 1930s, scientists developed safer, more effective vaccines to prevent prevalent diseases. Due to these developments anti-vaccine sentiment decreased from 1940 through the early 1970s. Reports of seizures due to DTP vaccine increased in the late 1970s and 1980s, culminating in the widely publicized documentary *DTP: Vaccination Roulette* in 1982 that generated increased distrust in the safety of vaccines. The increased media attention led to a number of lawsuits aimed at vaccine manufacturers causing some vaccine manufacturers to stop production. In an effort to protect the U.S. supply of vaccines, the National Vaccine Injury Compensation Program (VICP) was created in 1986, which triggered government conspiracy accusations by some anti-vaccine groups.

By the 1990s, the anti-vaccine movement had renewed vigor. The publication of a *Lancet* article in 1998 by Andrew Wakefield, in which a link between autism and the MMR vaccine was proposed, set the stage for arguments against the MMR vaccine and added preservatives such as the mercury-based thimerosal. Despite subsequent studies showing no association between vaccines and autism, the debate sparked the
“Green Our Vaccines” campaign\textsuperscript{227} which could be considered the main anti-vaccine movement of the 21\textsuperscript{st} century.

The “Green Our Vaccines” movement blames preservatives, adjuvants, and other contaminants in vaccines for a host of problems from asthma to autism. The argument is that if vaccine production was made cleaner and safer by removing components, particularly aluminum and the use of animal products, vaccines would cause fewer side effects, particularly neurologic disorders\textsuperscript{214,227}.

Recent introductions of new vaccines such as the pneumococcal conjugate vaccine and rotavirus vaccine have also lead to a “Too Many Too Soon” campaign\textsuperscript{214,223} which argues that the current vaccine schedule is overwhelming the child’s nascent immune system. Anti-vaccination groups argue that as the number of recommended vaccines has increased so has the incidence of not only neurologic but autoimmune disorders. These two arguments are the basis for the growing alternative vaccine schedule movement. The alternative vaccine schedule suggests avoiding vaccines with high levels of “contaminants” and spacing out vaccines to avoid overwhelming the immune system\textsuperscript{228-230}.

\subsection*{1.2.2 Anti-vaccinationist Belief Systems}

Those who oppose vaccination, particularly compulsory vaccination, are often called anti-vaccinationists and are extremely unified in their objection to vaccines. Most often anti-vaccinationist views are driven by one or more of three major ideologies: individualism, religion, and suspicion\textsuperscript{214,231,232}.

Individualists take the position that governments cannot mandate vaccination because vaccines do pose a risk, albeit minimal, to the individual. This ‘my body my
decision’ stance has grown as more vaccines are mandated for school entry, the perceptible risk of disease has decreased, and public campaigns have brought increased attention to perceived safety issues regarding vaccination. Recently, exemptions to mandatory school vaccination have increased, and larger increases have been seen in states allowing philosophical exemptions compared to states with religious but not philosophical exemptions.

Religious groups also have faith-based opposition to vaccination. Christian Scientists believe that medical interventions go against the word of God by violating the temple of the body. The Catholic Church has ethical objections to the use of human embryo cells, bovine serums, and green monkey kidney cells during the production of vaccines due to trace elements remaining in the final product. The Amish, while having no specific rules about immunization, have lower immunization rates. It is thought that their lower immunization rates, only 16% to 26%, is due to a combination of differing beliefs in health care and a lack of understanding regarding the benefits of vaccination. The use of religious exemptions, and the less stringent philosophical exemptions, to mandated school vaccines has increased in recent years creating pockets of unvaccinated children allowing for outbreaks of diseases, such as pertussis and measles.

Due to increased media attention since the 1980s, the most visible group of anti-vaccinationists may indeed be those who have a mistrust of government and/or pharmaceutical companies and thus are suspicious of vaccines. Well known groups such as Generation Rescue and the National Vaccine Information Center fall into this mistrust category because they claim the government is covering up the true adverse
events associated with vaccination\textsuperscript{214,223}. Some more radical views persist in this group as well, including the idea that the polio vaccine caused the HIV epidemic\textsuperscript{1,242} or the belief among some radical Muslims that vaccines are Westerners’ way of sterilizing Muslim men\textsuperscript{243}.

### 1.3 Alternative Vaccination Schedules

#### 1.3.1 The Middle Ground between Vaccinating and Not Vaccinating Children

The alternative vaccine schedule provides a middle ground between fully vaccinated and un-vaccinated that embraces vaccine-hesitant parents who still want to vaccinate their children. Alternative vaccine schedules incorporate messages from both the “green our vaccines” and the “too many too soon” anti-vaccinationist arguments\textsuperscript{218,219,228-231,241}. By reducing the number of vaccines given at one time or delaying vaccination until the child is older\textsuperscript{228-230}, alternative vaccine schedules address the anti-vaccine movement’s claim that children receive too many vaccines during the first years of life thus leading to a host of problems from asthma to autism and other neurologic disorders\textsuperscript{237,244}. Alternative vaccine schedules often address parent concerns about vaccine components including DNA and viral contaminants from the cell lines used to make some vaccines as well as adjuvants and preservatives added to vaccines to increase their efficacy and stability\textsuperscript{228,230}.

Parents who follow these alternative schedules often avoid specific vaccines or formulations, reduce the number of vaccines given at one time or overall, increase the spacing between each vaccination, delay vaccination until the child is older, or any combination of these strategies\textsuperscript{228-230,241}. Given differing opinions on the necessity and timing for each of the 15 recommended vaccines among those who endorse these
alternative schedules, parents have myriad options when choosing an alternative vaccine schedule. These options include schedules developed by physicians, parent groups, friends, and if they cannot find one to match their needs, parents can develop their own.

The growing discussion around alternative vaccine schedules (AVSs) in the blogosphere and on anti-vaccine websites has elicited strong responses from vaccine supporters. Opponents of AVSs remind parents and other AVS supporters that the current recommended schedule in the U.S. is based on the most recently available date for the safety and efficacy of these vaccines in concert with the other recommended vaccines in the schedule. Alternative vaccine schedule opponents also remind the public that the CDC and other organizations create schedules that are specifically developed to protect children when they are most vulnerable to serious sequelae from vaccine-preventable diseases. For instance, the pertussis vaccine is given starting at two months because children under one year are at increased risk of dying from the disease, as was evidenced in 2010 where 10 infant deaths due to pertussis occurred in California. Inadequate protection due to under-immunization leaves children vulnerable to vaccine-preventable diseases, and delaying or refusing specific vaccines leaves children vaccinated according to an alternative schedule at risk for catching and spreading these infections. Despite warnings from researchers and public health officials about the danger of under-immunization, some parents continue to consider these schedules as a means to assuage their fear of vaccines.
1.3.2 Published Alternative Schedules

While studies by Dempsey, et al., and Robison, et al., indicate that parents use alternative vaccines from a variety of sources\textsuperscript{175,215}, there are three popular physician-published alternative vaccine schedules often cited in the literature\textsuperscript{175,215,228-230,241,249}. These schedules were created by Drs. Robert Sears\textsuperscript{230}, Stephanie Cave\textsuperscript{228}, and Donald Miller\textsuperscript{229} and present three unique perspectives on alternative vaccination scheduling. While each of these physicians present a different perspective on which vaccines are necessary and why, their alternative vaccine schedules all incorporate three patterns: first, they reduce the number of vaccines given at each office visit, second, they delay some or all vaccinations until the child is older, and third, they suggest parents selectively refuse vaccines they consider controversial or unnecessary\textsuperscript{228-230}.

1.3.2.1 Dr. Sears

Dr. Sears has published two alternative vaccination schedules in his book \textit{The Vaccine Book: Making the Right Decision for Your Child}\textsuperscript{230}. This book offers advice to two types of parents, those who want to select specific “safe or necessary” vaccinations and those who worry that children get too many vaccines at each visit. While Dr. Sears describes his book as pro-vaccine, his book, which describes vaccines, their adjuvant (additional components) and each vaccine’s relationship with the diseases it prevents, has been offered up by anti-vaccine supporters as proving there is something “wrong” with vaccines\textsuperscript{230}.

Dr. Sears believes that not all vaccines are equally important given the risk of disease in the U.S., thus he has created a schedule that delays controversial vaccines while vaccinating on time for those diseases Dr. Sears considers most important. The
alternative vaccination schedule set forth by Dr. Sears recommends specific manufacturers, dosing, and scheduling so that children are up-to-date according to the recommended schedule by school entry. However, he caters to much more hesitant parents by recommending a selective alternative vaccine schedule which only includes those vaccines Dr. Sears considers most important.  

While ACIP recommends up to 6 vaccines in one visit, Dr. Sear’s alternative schedule recommends that children get no more than 2 vaccines at any given time. Therefore instead of visiting a doctor at 2, 4, 6, 12, 15, 18 and 59 months, children should visit the doctor monthly from 2 to 9 months then at 12 months, 15 months, 18 months, 2 years, 2.5 years, 3 years, 3.5 years, 4 years, 5 years and 6 years. Thus, the visit schedule is expanded from 8 to 17 (excluding flu vaccine). Children will be up-to-date according to the ACIP-recommended schedule by 6 years of age, 12 months behind other children (see Appendix 5 for complete alternative schedule).  

Dr. Sears developed his AVS for parents who would normally have declined all vaccines and thus only includes vaccines that protect against diseases that have severe outcomes or are common, and the vaccines have few “controversial ingredients” and “low reactivity”. Thus this schedule includes: diphtheria, tetanus, and pertussis (a severe disease); *Haemophilus influenzae* type B (a severe disease), pneumococcal conjugate vaccine (a common disease), and rotavirus (a common disease). While Dr. Sears starts his AVS at two months, he also offers alternatives that start at six months, one year, and two years, thus appealing to a large audience. In 2009 he sold over 40,000 copies of his book.
Dr. Sears specifically recommended splitting the MMR vaccine into its original components in both the alternative and selective schedules. However, in 2009 he offered an addendum as Merck & Co., Inc. stopped production of individual components. His addendum suggests that hesitant parents wait until a child is 4 years of age to receive the vaccine, although starting any time after 1 year is acceptable to him 230.

1.3.2.2 Dr. Cave

Dr. Stephanie Cave’s book *What Your Doctor May Not Tell You About Children’s Vaccinations* 228 focuses not only on vaccines but on the laws and regulations surrounding vaccine development, administration, and adverse events. She has developed a vaccination schedule which begins at 4 months and includes only diphtheria, tetanus, and pertussis vaccine, *Haemophilus influenzae* type B vaccine, and inactivated polio vaccine until 15 months where she introduces other vaccines one at a time 228 (see Appendix 6, for full schedule).

In addition to her alternative vaccination schedule, Dr. Cave recommends that children not be vaccinated if they are showing any signs of infection or cold (e.g., fever, runny nose, cough, etc.), that all vaccines given be thimerosal-free, and that separate vials of measles, mumps, and rubella be given, not as MMR, but separately months apart. Dr. Cave also does not believe in boosters unless a child’s vaccine titers indicate a lack of immunity. Finally, Dr. Cave recommends a series of vitamins before each vaccination, including increased Vitamin C and Vitamin A, ostensibly to boost immunogenicity 228.

While her vaccination schedule is similar to Dr. Sears in the overall reduction of vaccines at each visit 228;230, Dr. Cave is against vaccination in general and promotes not vaccinating children. Some of her recommendations are out of date; currently in the U.S.
it is virtually impossible to separate the components of DTaP and MMR. Further, the FDA recommended the removal of thimerosal from vaccines given to children under 6 years in 1999 (and reiterated this recommendation in 2000). Currently only Tripedia and some flu vaccines, but not the live nasal vaccine, contains trace amounts of thimerosal.

1.3.2.3 Dr. Miller

Dr. Donald Miller openly opposes many vaccines. Dr. Miller’s theories contend that too many vaccines given too early in life are the basis for many neurological disorders. Thus, he recommends parents should not begin vaccinating before two years of age and avoid all vaccines that contain live viruses (MMR, varicella, live polio (no longer used in the U.S.), and intranasal flu vaccine), all flu vaccines, hepatitis B, PCV, and Hib. According to Dr. Miller’s schedule the following vaccines should be given one at a time starting at twenty-four months of age and separated by at least six months: pertussis, diphtheria, tetanus, and polio (Salk vaccine only). Dr. Miller contends that adequate diet and herd immunity will protect children from the other vaccine-preventable diseases. It is also indicated that having these diseases is a natural part of the human experience and will build a stronger immune system. Other vaccines specifically not mentioned (hepatitis A, rotavirus, and meningitis) are left up to parent’s discretion but are discouraged (Appendix 7).

While Dr. Miller’s schedule varies significantly from Dr. Sears as he specifically recommends against vaccination, he shares some similarities with Dr. Cave. Both feel that all combination vaccines should be separated, although this can no longer be done in the U.S.
1.3.3 Use of Alternative Schedules in the United States

Use of alternative vaccine schedules in the U.S. is not well documented. While less than 1% of children are totally unimmunized estimates of the number of children following an AVS are between 10 and 25% . These estimates do not include children who are considered off schedule due to a number of reasons including missed visits, illness, incorrect records, or vaccine shortage. Despite the availability of multiple physician-published AVSs , two recent studies indicate that few parents directly follow one of these schedules . Dempsey, et al., estimated parents choosing one of these physician-published alternative vaccine schedules to be only 0.6% of the population whereas parents choosing any alternative vaccination schedule was about 8% of the population .

Individualized AVS use leads to a lack of clear definitions. Parents following an AVS may blend strategies: delay vaccination, reduce the number of vaccines given at each visit, refuse specific vaccines, and/or split combination vaccines into their constituent antigens . Multiple AVS patterns result. The need to classify children clearly on an AVS distinctly from children being off schedule due to other issues (e.g., vacations, illness, vaccine availability) substantially complicates the true picture.

A more recent study by Robison, et al., found that in 2009, 9.5% of children aged 2 to 9 months in Portland, Oregon, were on a vaccination schedule that exhibited shot-limiting behavior with only two or fewer injections at one time; this proportion increased to almost 40% when children who had occasional shot limiting behavior were added . This additional 30.5% of parents may include those who are off-schedule due to other reasons discussed previously, thus compounding the problem of distinguishing off-
schedule from AVS use\textsuperscript{175}. Parent and physician acceptance of these schedules and the reasons they may choose to vaccinate a child according to an AVS are important in understanding the impact of alternative vaccination schedules on today’s society.

1.3.4 Parental Views on Alternative Scheduling

Recent studies published in 2011 have shown that 13% of parents did not think their child received all vaccines according to the ACIP schedule and 8% of parents said they were intentionally vaccinating off schedule, but less than 1% of parents indicated using a known alternative vaccine schedule\textsuperscript{215}. Parents are turning to AVSs because of concerns about vaccine safety, efficacy, and necessity\textsuperscript{181}. Studies suggest that parents are increasingly engaging in discussions with physicians about vaccination. This need for information leads parents to internet searches, the results of which yield conflicting information about vaccines\textsuperscript{223}.

Parents who follow an AVS do so out of concern about the information they receive about vaccines from many sources including other parents, media internet etc.\textsuperscript{214}. These parents still believe in vaccination but to assuage their fears look for an alternative method that is “safer” than the current recommended schedule. Parents using AVSs sometimes feel that the risks associated with “natural” disease is better in some cases compared with the risk of vaccination\textsuperscript{228,230}. Overall, these parents recognize the benefit of vaccination but choose to delay or refuse some vaccines based on their own risk-benefit analysis.
1.3.5 Physician Views on Alternative Scheduling

While parents may choose to develop an alternative schedule for their child based on internet and social media research, the most noted alternative schedules have been developed by pediatric physicians Sears, Cave, and Miller \(^{228-230}\). This would give the impression that at least some physicians are against the current recommended schedule. Even physicians who agree with the schedule may comply with a parent’s wishes that the child be vaccinated according to an AVS in order to confer at least some immunity \(^{197}\).

The American Academy of Pediatrics specifically indicates that physicians should not turn away children based on the vaccination preferences of parents, although studies suggest that only 64% of physicians are comfortable administering these alternative vaccination schedules \(^{197}\). Physicians in public clinics were less comfortable than private physicians with administering an alternative schedule (OR 0.12 95% CI: 0.03-0.53) \(^{197}\). The increased willingness of private physicians to administer alternative schedules may be due to continuity of care and/or the ability of private physicians to ensure parents add the necessary visits to keep a child UTD \(^{197}\).

1.3.6 Impact of Alternative Scheduling on UTD Status

The risk of vaccine-preventable disease is not consistent throughout childhood and the ACIP vaccine recommendations take into account this variable risk by promoting vaccination as early as is safely possible \(^{252}\). Thus, it is thought that the AVS, which often spreads vaccines over a longer period of time, exacerbate health inequalities as parents with high socioeconomic status are more likely to afford the costs associated with extra visits \(^{175;188;215;230}\). This is in direct contrast however, with the study by Dempsey, et al., that found that alternative schedules are associated with a lack of consistent health care
The use of alternative schedules also leads to concerns about appropriate timing. A study by Hamlin, et al., found that 31% of children with multiple or inconsistent providers had inappropriately timed vaccinations.

Another concern is the increased risk associated with under-vaccination. While some schedules, such as Dr. Sears’ alternative schedule, will have children UTD by age six, adherence to other selective/alternative vaccine schedules will mean that children are never considered UTD as they abstain from specific vaccinations. Studies have shown that children who are under-vaccinated are at a significantly increased risk of contracting diseases such as pertussis or measles. Children who are vaccinated in a mostly unvaccinated community are at a higher risk of contracting vaccine-preventable diseases due to the potential for vaccine failure and increased likelihood of transmission from an unvaccinated population. It is unknown if the same effect will be seen among communities with large proportions of alternative schedule users, although it stands to reason that large numbers of under-vaccinated children will pose similar risks of infection.

1.4 Vaccination Registries and Immunization Information Systems

1.4.1 Overview of Immunization Registries and Immunization Information Systems

Immunization registries are defined as “confidential, population-based, computerized systems for maintaining information regarding children’s vaccinations.” The main focus of immunization registries is to create a public and private sector collaboration to reduce fragmentation of records in the health care system thus allowing for more complete assessment of vaccination coverage. While it would seem a
national database could further decrease fragmentation, the National Vaccine Advisory Committee has supported regional registries instead of a national registry due to the differing needs of regions throughout the U.S. \(^254,256\).

Immunization registries have the capability of allowing physicians, public health officials, schools and parents access to a centralized database with the ability to assess both individual and community vaccination coverage, although not all registries allow access to all groups. Physicians can utilize the built-in systems to determine the appropriate vaccines to administer at an office visit, send reminders to parents that vaccinations are due, and print out vaccination reports for parental records, and manage vaccine inventory \(^255-257\). Allowing schools access to an immunization registry streamlines the assessment of school vaccine eligibility requirements \(^257\). From a public health standpoint, immunization registries not only help improve vaccination coverage by identifying children who are under-vaccinated, but also help reduce the costs associated with over-vaccination due to inappropriately timed or unrecorded doses \(^255-257\).

In an effort to increase the usability of immunization registries, other electronic resources are being combined into a single interface creating what is called an Immunization Information System (IIS) \(^256\).

1.4.2 Combining Immunization Registries with other Electronic Sources

Many immunization registries focus on easing the burden of vaccine data entry by integrating electronic health information such as the electronic medical record. Studies have indicated that the use of electronic billing records to populate an immunization registry reduces the accuracy of the immunization registry; in fact, entering data from billing records can account for nearly 50% inaccuracy in the data entry process \(^258-260\). In
contrast, the use of electronic medical records significantly improved the accuracy of reporting and the number of children entered into the system overall. In addition to merging electronic medical records and immunization registries or IIS, others advocate greater integration of childhood health information systems. These childhood health information systems create a single interface containing information stored in individual databases such as vital records, newborn screening, early hearing detection and intervention, immunization registries, lead screening data, and social services such as Woman Infant and Child services (WIC). The proposed creation of these childhood health information systems would allow users a single location to assess the overall health status of the child and, if properly implemented, would enable easy linking such as a single entry page that updates demographic information across the system rather than just at the point of service.

Progress in the U.S. toward these integrated child health systems is underway. A survey of 18 states indicated that many have developed the ability to launch vaccine coverage interventions using data from these systems despite technical start up issues.

1.4.3 Completeness of Registries in the U.S.

The ability to assess vaccination coverage using immunization registries relies on a basic level of completeness for data entered into the system. The Healthy People 2020 guidelines include a goal of having 95% of children under age 6 with full vaccine histories entered into a functional immunization registry complemented by at least 80% provider participation. Currently, national statistics from 2008 show that 75% of children have at least 2 vaccines entered in an immunization registry and 80% of public
providers and 38% of private providers are submitting data into an immunization registry 258.

Immunization registry coverage is associated with increased provider use and timely reporting 259-261;268-270. A study in Bexar County, Texas found that immunization registries are more accurate than paper charts in regions with good provider participation 268. Low provider participation can decrease the accuracy of an immunization registry, as in Philadelphia where the registry misclassified almost 18% of children as not UTD 269. A Denver-based immunization registry was able to increase vaccine reporting from 71.4% to 97.7% in a three year span by providing physician practices with technical support and promoting point of service data entry 259. Provider participation can also be increased by linking the immunization registry with other functions such as the VFC program and the blood lead database 263;264.

1.4.4 Research Using Registries

As registries become more mature in their development, leveraging immunization records for more than maintaining vaccine coverage has become a shifting priority 255;262. Few studies have utilized immunization registry data for purposes other than immunization registry accuracy and overall vaccination coverage 271;272. A study utilizing immunization registries to determine vaccine effectiveness found that reliability of data and inability to accurately match children in multiple databases was problematic. However, surveillance studies using immunization registries have successfully shown uptake of new vaccines 273 and tracked the impact of vaccine shortages 271. Immunization information systems with increased demographic information have demonstrated that immunization registry reminder/recall capabilities can improve vaccination rates and
decrease overall coverage disparities\textsuperscript{270,273}. As research utilizing registries increases it will be important to define the limitations of individual registries in terms of accuracy and coverage; nevertheless, registries should be utilized to increase our understanding of vaccination coverage and practices.

\textbf{1.4.5 The New York State Immunization Information System (NYSIIS)}

New York State maintains two major immunization information systems: the Citywide Immunization Registry (CIR) which covers children who reside within the 5 counties of New York City and the New York State Immunization Information System (NYSIIS) which includes all children residing in New York State outside of NYC. The NYSIIS began as a voluntary system for providers outside of NYC in 1994 and was based on the regional registries HealthyShot and the Immunization Registry Information System (IRIS). The original voluntary registry was a software-based system and required individual parental consent for children to be entered into the system. To increase coverage of this original voluntary system, New York State passed legislation in 2006 to create a web-based statewide system which included mandatory participation for all providers giving immunizations to children under 19 years of age\textsuperscript{274}.

Healthy People 2020 set several benchmarks for IIS including that at least 90% of children age six years and younger have at least two vaccinations recorded in an IIS\textsuperscript{267}. As of 2012 it is estimated that 88% of children 6 years of age and younger have at least 2 immunizations entered NYSIIS. The proportion of children age six years and younger who have at least two vaccines recorded in NYSIIS ranges from 66.1% to 97.6% regionally with higher proportions in upstate NY compared to the areas surrounding NYC. The registry includes a total of 3.7 million children and over 43.4 million
immunizations. Data is entered and utilized by health care provider practices, pharmacies, local and state departments of health, and health plans. Currently about 20% of practices submit data through electronic data exchange, however, these accounts for 60% of the information being uploaded to NYSIIS, likely increasing the accuracy of information.

1.5 Proposed study and study objectives

1.5.1 Motivation and rationale for proposed study

The CDC lists vaccination as one of the top ten public health achievements of the 20th century\textsuperscript{275}; incidence of vaccine preventable diseases has declined by over 90% for diseases such as diphtheria, tetanus, pertussis, and poliomyelitis\textsuperscript{276}. Despite these successes, there has been increasing media attention given to the safety and efficacy of vaccines\textsuperscript{212}. Young parents are increasingly turning to the internet for information about vaccines, where they encounter a myriad of anti-vaccine websites and blogs discussing the dangers of vaccination\textsuperscript{187;191;214}. Thus, it is no surprise that vaccine hesitancy among parents has been increasing in the past two decades\textsuperscript{187-189;206;211}. Vaccine-hesitant parents believe that vaccines are unsafe, ineffective, and unnecessary in an age with a historically low incidence of vaccine-preventable disease\textsuperscript{188;189;206}. Studies in the late 20th and early 21st centuries focused on vaccine refusal, including un-vaccinated children and selective refusal, particularly among young, school-age children; and the impact on vaccine coverage and incidence of disease\textsuperscript{178;180;181;184;277-279}.

Growing concern over the increasing number of recommended vaccinations\textsuperscript{194;204;208} and the ingredients in vaccines\textsuperscript{214;230} led vaccine-hesitant parents to begin modifying the RVS for their children. These alterations include delaying vaccination,
reducing the number of vaccines given at one time, and increasing the time between vaccination visits. While the term “Alternative Vaccine Schedule” did not appear in the literature until 2007 when Dr. Robert Sears published his book on vaccines, studies were already noting that intentional delay of vaccine administration was having an impact on vaccine coverage and incidence of disease.

While physicians remain the most trusted source for recommending vaccination among vaccine-hesitant parents, a small but growing number of physicians remain personally vaccine-hesitant. Given that 79% of physicians report parent refusal of vaccine and 89% at least one request to delay or spread out vaccination in the average month, it is important to address misconceptions among clinicians. The time required to counsel vaccine-hesitant parents is reported as the biggest burden associated with increasing requests for AVS. Consequently, some physicians are accommodating requests for alterations to the RVS as a compromise position. In some cases, providers suggest the use of AVS to parents. Opponents of AVS argue that by accommodating parents, physicians are sending the message that these schedules are acceptable when in fact no studies have determined the safety and efficacy of altering the RVS.

Differentiating children following an AVS from children who are off-schedule due to external factors (e.g., lack of access to care, missed appointments) is problematic. While researchers agree that AVS is defined broadly as an intentional deviation from the RVS, the wide variation in AVSs makes standardized classification difficult. Identification of AVS is further complicated by a lack of specificity in the RVS (e.g., age ranges rather than specific ages for vaccination).
Few studies have sought to identify the prevalence of AVS in the U.S. The use of AVS leaves children vulnerable to vaccine preventable disease\textsuperscript{246,247,280}, thus establishing the prevalence and profile of children vaccinated following an AVS is important for maintaining vaccination coverage. The objective of this project is to identify and describe children in New York State (NYS), outside New York City (NYC), who are vaccinated following an AVS. The purpose is to estimate: 1) the prevalence of AVS in NYS, excluding NYC; 2) the individual and community characteristics associated with the use of AVS; and 3) the practice characteristics of providers who vaccinate children following an AVS. The motivation for this study is two-fold. First, the development of a method to identify children following an AVS using vaccination histories will aid in the future study of AVS adoption. Second, the identification and description of children vaccinated following an AVS and the providers who vaccinate them will help inform educational strategies to address persistent concerns and increase vaccine coverage.
Chapter 2.  Methods

2.1  Research questions and specific aims

2.1.1  Research question 1 – Prevalence of alternative vaccination schedule use in New York State outside of New York City

Research question:  What percentage of children in New York State, outside New York City, are being vaccinated according to an alternative vaccination schedule?

Specific aim 1-1:  Determine the number of children under 9 months, with vaccines recorded in NYSIIS, who are vaccinated following the recommended schedule or consistently vaccinated with a pattern not consistent with the recommended schedule (Alternative Vaccination Schedule).

Specific aim 1-2:  Compare vaccination characteristics (e.g., age at first vaccination visit, number of vaccination visits, up-to-date status) between children vaccinated following recommended and alternative vaccination schedules.

Specific aim 1-3:  Map the proportion of children vaccinated following an alternative vaccination schedule by county for New York State, outside New York City.

2.1.2  Research question 2 – Demographic and neighborhood factors associated with alternative vaccination schedules

Research question:  What are the demographic and neighborhood factors associated with the use of alternative vaccination schedules?

Specific aim 2-1:  Determine individual and neighborhood factors that are associated with use of AVS through linking census data and NYSIIS data.

Specific aim 2-2  Map the proportion of children vaccinated according to an alternative vaccination schedule by zip code.
2.1.3 Research question 3 – Distribution of children following an AVS by physician practice in New York State, outside of New York City.

Research question: Are children on an AVS clustered at specific practices in New York State, outside New York City?

Specific aim 3-1: Determine the proportion of children at each practice who have not received at least one dose of each recommended vaccine, among children who have at least one vaccine recorded in NYSIIS.

Specific aim 3-2: Determine the proportion of children at each practice who are being vaccinated according to the recommended and alternative vaccination schedules, among children who have received vaccines.

2.2 Study methods

2.2.1 Study Data

In 2008, NYS Public Health Law 2168 mandated that all vaccinations given to persons under 19 years of age, residing in NYS exclusive of NYC, be entered into NYSIIS. In addition to entering new vaccinations, practices were asked to enter historic vaccination data for any child receiving a vaccination in NYS after January 1, 2008. To facilitate data entry and reduce duplication, NYS vital records information for all children born January 1, 2004 and later is pre-populated into the system daily. Physicians with electronic medical records (EMR) can link their records with NYSIIS or manually enter vaccine data through the web-based interface. The system contains entries for each vaccination delineated by a unique client identification number which makes it possible to determine the child’s vaccination history over time.

The New York State Department of Health, Bureau of Immunization provided information contained in NYSIIS on all vaccinations given to children 19 years of age
and younger residing in NYS, outside NYC, on May 10, 2012. The information provided includes the unique client identification number, unique practice identification number, date of administration, type of vaccine and other information (Appendix 8) for each vaccine administered.

Since the entry of data into the NYSIIS is mandated by law and contact information for children with information in the system was not provided, informed consent from parents and assent from children was not obtained. The institutional review board for the New York State Department of Health approved this study (Appendix 9 NYSDOH IRB).

2.2.2 Determining Alternative Vaccination Schedule Prevalence – Paper 1
2.2.2.1 Study Population

All children born between January 1, 2009 and August 14, 2011, with vaccinations recorded in NYSIIS as of May 10, 2012, were initially selected for analysis (N=337,945). Children were excluded if their NYSIIS-recorded county of residence was NYC (N =18,461) or outside NYS (N=119); children were also excluded if their only NYSIIS-recorded immunization was a single dose of hepatitis B vaccine (HepB) administered in the first 41 days of life with no other vaccinations recorded by 270 days (9 months) of age (N=45,479). The majority of these children had a single vaccination of HepB at birth recorded in NYSIIS (N=25,829). Data for vaccination visits through 270 days of age were extracted for analysis; doses of HepB administered in the first 7 days were considered a birth dose and were excluded from analysis.
2.2.2.2 Vaccine Schedule Grouping

Vaccine histories for children eligible for the study (273,886 children) were assessed for vaccination patterns in comparison to the ACIP-recommended schedule (RVS). The number of vaccines in each series is affected by formulation differences, such as with rotavirus vaccine (RV) and *Haemophilus influenza* type b vaccine (Hib). The number of vaccines recommended on each visit varies due to scheduling age ranges, such as with HepB (the second dose is recommended to be given between 1 and 2 months and the third dose is recommended to be given between 6 and 18 months) and the third dose of inactivated poliovirus vaccine (IPV) (recommended to be given between 6 and 18 months of age). In general, the RVS recommends that by 9 months of age children should receive 2-3 doses of HepB, 2-3 doses of RV, 3 doses of diphtheria/tetanus/acellular pertussis vaccine (DTaP), 2-3 doses of Hib, 3 doses of pneumococcal conjugate vaccine (PCV), and 2-3 doses of inactivated polio vaccine (IPV) at 3 scheduled visits around 2, 4, and 6 months of age. According to the RVS, children would receive between four and six vaccines at the 2 and 4 month visits, and at least two vaccines at the 6 month visit. If all recommended vaccines are given at the earliest recommended time in three visits at two, four, and six months of age children will receive six vaccines on the first visit, five vaccines on the second visit, and four or more vaccines on the third visit, based on formulation differences.

For purposes of this evaluation, vaccination coverage was considered separately for each vaccine which is available in a single disease-specific formulation (i.e., HepB, RV, Hib, PCV, and IPV) and for DTaP, which prevents three diseases but is not available in single disease-specific form. Receipt of combination vaccines was counted as the total
of the unique study-specific vaccines contained (e.g., Pentacel which contains DTaP-Hib-IPV was considered three vaccines; Comvax, which contains Hib-HepB was considered two vaccines, etc.).

Children who had at least three vaccine visits where five or more vaccines were administered were considered to be vaccinated following the RVS. Children were also considered to be following the RVS if they had at least two visits where five or more vaccines were administered and no more than four visits, regardless of the number of vaccines given on the third and fourth visit.

Children not following the RVS were classified according to one of three possible AVS patterns: 1) restrictive schedule, where four or fewer vaccines were administered at all vaccination visits effectively restricting the number of vaccines given per visit; 2) selective schedule, where the child did not receive at least one dose of a recommended vaccine; or 3) restrictive and selective schedule where the number of vaccines administered was reduced and specific vaccines were selectively refused.

Children who did not fit any of these patterns were classified as following an unknown vaccination schedule.

2.2.2.3 Assessment of Up-To-Date Status

Given differences in the RVS, children were considered up-to-date (UTD) for the recommended vaccinations at nine months (270 days) if they had received the following doses: 1 HepB, 2 RV, 3 DTaP, 2 Hib, 3 PCV, and 2 IPV. Because the birth dose of HepB was not utilized for analysis and the 6-month HepB dose can be given any time between six and 18 months, children with one dose of HepB were considered UTD. Similarly,
children with only two doses of IPV were considered UTD due to the 6 to 18 month recommended age range for the third dose. Children were considered UTD for RV and Hib with two doses because the formulation of these vaccines could not be determined.

2.2.2.4 Statistical Analysis

Age at first vaccination visit, defined as the first visit after 41 days of life or the first visit with a vaccine other than HepB, and the number of vaccination visits from the first visit to 9 months of age (270 days) were assessed for all children in the study (N=273,886). The proportion of children in each vaccination schedule group (AVS, RVS, unknown) and the proportion of children on an AVS in selective, restrictive, and restrictive/selective groups were calculated. The proportion of children considered UTD at nine months and age at first visit were compared by vaccination schedule group using 2-sided chi-square tests ($\alpha=0.05$). The number of visits and the time from the first vaccination visit to UTD status were compared among the vaccine schedule groups using two-sided ANOVA tests or equivalent non-parametric tests where appropriate ($\alpha=0.05$). County-specific percents of children following an AVS were calculated utilizing all children classified as not following an AVS (RVS and Unknown) in the denominator. All analyses were completed using SAS 9.2 (SAS Institute, Inc, Cary, NC).

2.2.3 Determining Community Based Characteristics of Alternative Vaccine Schedule Users – Paper 2

2.2.3.1 Study Population

All children born between January 1, 2009 and August 14, 2011, with vaccinations recorded in NYSIIS as of May 12, 2011, were selected for analysis. Children were excluded if their NYSIIS-recorded county of residence was NYC or
outside NYS; children were also excluded if their only NYSIIS-recorded immunization was a single dose of HepB administered in the first 41 days of life with no other vaccinations recorded by 270 days (9 months) of age. The majority of these children had a single vaccination of HepB at birth recorded in NYSIIS. Data for vaccination visits through 270 days of age were extracted for analysis; doses of HepB administered in the first 7 days were considered a birth dose and were excluded from analysis (See section 2.2.1 and 2.2.2.1 for further detail).

The vaccination schedule followed by each child was determined as described in section 2.2.2.

2.2.3.2 Individual and Neighborhood Demographic and Socio-economic Measures

Individual demographic information contained within NYSIIS is limited but includes: date of birth, gender, zip code or county of residence, and number of practices administering vaccines. The distance traveled to the most frequent provider was approximated by calculating the linear distance from the centroid of the zip code of residence to the centroid of the practice zip code where the child had the most unique vaccination dates.

Neighborhood level demographic and socioeconomic factors were obtained from the American Community Survey (ACS)\textsuperscript{282}. The ACS provides 5 years estimates, from 2007-2011, at the zip code level within NYS for demographic and socio-economic indicators. These indicators include median household income for the past 12 months (in U.S. dollars), percent of persons living below poverty, unemployment rate for persons 16 and older, the GINI income coefficient (a measure of income diversity), percent of
residents who are: non-Hispanic white, non-Hispanic black, Asian, and Hispanic, percent of households with children, and percent of persons age 25 and older with a bachelor’s degree or greater.

To obtain information on the urbanicity of each zip code in NYS, rural-urban commuting area (RUCA) codes were obtained from the United States Department of Agriculture Economic Research Service. Rural-Urban commuting area codes were classified as urban (codes <3), suburban (codes 3 - <7), and rural (codes 7+).

2.2.3.3 Statistical Analysis

The association between individual demographic characteristics provided in NYSIIS (e.g. gender, year of birth, number of providers, approximated distance traveled to provider) and vaccination following an AVS was determined using log binomial regression to calculated unadjusted risk ratios. Adjusted risk ratios for the association between individual characteristics and vaccination following an AVS were also calculated with all individual level variables using a multivariable log binomial regression model.

The number of children residing in each NYS zip code and the number of children following an AVS in each zip code was calculated from individual level NYSIIS data. To better understand the association between demographic and socio-economic characteristics not available through NYSIIS these aggregate values were matched to ACS and RUCA data based on NYS zip code. The number of children vaccinated following an AVS in each NYS zip code was modeled using poisson regression analysis to determine an unadjusted rate ratio. Adjusted rate ratios were determined by placing all
zip code level demographic and socio-economic data into a multivariable poisson regression. Spearmans correlation coefficients were calculated between the proportion of children following an AVS in each zip code and all zip code level demographic and socio-economic variables. All analyses will be completed using SAS 9.2 (SAS Institute, Inc, Cary, NC).

2.2.4 Characteristics of Medical Practices Serving Children Vaccinated Following an Alternative Vaccination Schedule – Paper 3

2.2.4.1 Study Population

Physician practices in NYS outside of NYC reporting vaccination within 270 days of birth for children born between January 1, 2009 and August 14, 2011 as of May 12, 2012

2.2.4.2 Assignment of children to a medical practice

The vaccination schedule of each child was determined as described in section 2.2.2 before children were assigned to a primary practice.

The administering practice (e.g., clinic, hospital, Department of Health) for each vaccination recorded in NYSIIS is documented using a unique practice identification number. Excluding the HepB birth dose given in the first 7 days, the majority of children (91%) have vaccinations administered at only one practice by 270 days of life. The remaining children have vaccinations listed at two to four separate practices. Children were assigned to the medical practice reporting the most unique vaccination dates. If the same number of unique vaccination dates were reported by different
practices, children were be assigned to the most recent reporting practice. The practice to which children were assigned was considered to be their primary practice.

2.2.4.3 Physician-related variable creation

The size of each practice was determined be based on the number of children assigned to each practice as described in section 2.2.4.2. Using the number of children reported by a practice as the denominator; the proportion of children who are: up-to-date; missing a recommended vaccine (HepB, RV, IPV, DTaP, PCV, Hib); following the recommended, alternative, or unknown schedule; and utilizing a selective, restrictive, or selective/restrictive schedule, were calculated for each practice.

2.2.4.5 Statistical Analysis

The association between the proportion of children receiving each recommended vaccine, proportion of children on an AVS, and type of practice will be determined using ANOVA or appropriate non-parametric analysis for all practices reporting information to NYSIIS (see section 2.2.4.1). All analyses will be completed using SAS 9.2 (SAS Institute, Inc, Cary, NC) with a two-sided alpha value of 0.05.
Chapter 3. Results

The results of research questions 1-3 are presented as three papers. Paper 1, entitled “Vaccinating My Way: Use of Alternative Vaccination Schedules in New York State” addresses research question 1 and aims 1-1 to 1-3. This analysis found that one in five children in NYS, outside NYC, is likely following an AVS. Children following an AVS had more vaccination visits and were less likely to be up-to-date for age appropriate vaccinations at 9 months. In addition, it took an average of 5 additional weeks for the children on an AVS to achieve up-to-date status by 9 months of age.

Paper 2, entitled “Community-based Characteristics of Children Following an Alternative Vaccine Schedule” addresses research question 2 and aims 2-1 and 2-2. This community-oriented analysis found that increased rates of AVS use were associated with a higher median income and educational status.

Paper 3, entitled “Reporting of Alternative Vaccine Schedule Use at Medical Practices in New York State” addressed research question 3 and specific aims 3-1 to 3-3. The results from this final analysis indicated that small urban practices vaccinated higher proportions of children following an AVS. Results of the third analysis also found that children not receiving rotavirus were more likely to be vaccinated in small, rural medical practices.
**Abstract**

*Background:* In the United States, historically high infant vaccine coverage has substantially reduced incidence of many once common childhood diseases. However, vaccine refusal or intentional deviations from the recommended vaccine schedule may create pockets of un/under-vaccinated children that can negatively impact herd immunity.

*Methods:* To quantify the proportion of children following an individually designed vaccination schedule (IDVS) a cohort study was conducted among children born in New York State, outside New York City, between January 1, 2009 and August 14, 2011. Children who by 9 months of age had at least one vaccination recorded in the statewide mandatory immunization information system after 41 days of age were classified as either attempting to conform to the Centers for Disease Control and Prevention published recommended vaccination schedule (RVS) or IDVS. The number of vaccination visits and up-to-date status at age nine months were compared between groups.

*Results:* Of the 273,886 children studied, the proportion of children following an IDVS was 24%. These children were significantly less likely to be up-to-date at age 9 months (12%) compared with those conforming to the RVS (84%, p<0.05). Among children following an IDVS who were up-to-date at age 9 months, an additional 47 days were needed to become up-to-date (175 vs. 128 days, p<0.05).
Conclusions: Almost one in four children in this study appear to be intentionally deviating from the RVS. Intentional deviation leads to poorer vaccination coverage leaving children vulnerable to infection and increasing the potential for vaccine-preventable disease outbreaks.
INTRODUCTION

The United States childhood vaccination program has achieved coverage proportions of 90% or greater for vaccines against diphtheria, tetanus and pertussis; poliovirus; measles, mumps and rubella; hepatitis B; pneumococcal disease; and varicella. The Advisory Committee on Immunization Practices (ACIP) provides a recommended vaccine schedule (RVS) covering 15 vaccine-preventable diseases for children six years and younger. This schedule is published by the Centers for Disease Control and Prevention (CDC) and endorsed by the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP). The CDC estimates that these vaccines prevent approximately 42,000 deaths and $83 billion in direct and indirect costs in each US birth cohort. Despite these successes, today’s parents may have more concerns about the safety of the RVS than the risk of disease due to the current low incidence of vaccine-preventable disease in the United States.

Vaccine safety concerns have lead parents to deviate from the RVS and pursue what are often referred to as alternative vaccine schedules (AVS). While several published versions of these schedules exist, studies have shown that most parents opt for a more individualized AVS approach. Despite the variability in AVS approaches; three predominant patterns have emerged including: delay of vaccines or particular doses, selective refusal of specific vaccines, and a reduction in the number of vaccines given at each visit. Today’s parents are blending these three tactics into what can be called an individually designed vaccination schedule (IDVS).
The number of children vaccinated according to an IDVS has been increasing in recent years. Studies estimate that intentional deviation from the RVS conservatively ranges from 10% to 13% of U.S. children; however, a survey of parents has shown that parental doubt in vaccines is higher, around 28%, indicating the potential for continuing increases in the use of IDVS. The increasing trend in intentional deviation from the RVS has prompted questions regarding the effects of these deviations on under-vaccination, disease risk, and the safety and effectiveness of these new vaccine patterns. Before these concerns can be addressed, a clear method for distinguishing children clearly following and IDVS from children who are off schedule for other reasons, (e.g., vacations, illness, vaccine shortage) must be adopted. The RVS has a period of intense, uniquely scheduled recommended vaccinations for children age 2 to 9 months which allows for an assessment of clear patterns related to IDVS.

Universal statewide childhood immunization registries provide an important opportunity to develop population estimates of the proportion of children following an IDVS. This study uses a statewide immunization registry to develop a conservative population estimate of the proportion of children age 2 to 9 months appearing to follow an IDVS (e.g., repeated refusal of a specific vaccine and repeated restriction of the number of vaccines provided in a single visit).
METHODS

Study Population

Vaccinations given to children younger than 19 years of age in New York State (NYS), outside of New York City (NYC) are required, under Public Health Law 2168, enacted in 2008, to be reported to the New York State Immunization Information System (NYSIIS). In 2011, more than 90% of practices providing vaccines to children were actively entering data into NYSIIS. At least two vaccines are recorded in NYSIIS for 88% of children younger than six years of age.

Vaccination records in NYSIIS for children born between January 1, 2009 and August 14, 2011 up to age 270 days (9 months) were initially selected for this analysis (N=337,945) on May 10, 2012. Children were excluded if 1) their NYSIIS-recorded county of residence was NYC (N =18,461) or outside NYS (N=119) or 2) their only NYSIIS-recorded immunization within the first 9 months was a single dose of hepatitis B vaccine (HepB) administered in the first 41 days of life (N=45,479). These early HepB doses were excluded because they are often given in the hospital and may be less influenced by parental concerns; lack of further vaccination also indicates that a child may not be receiving vaccination in NYS, outside of NYC. Doses of hepatitis B given in the first 7 days were excluded from analysis; all other NYSIIS recorded doses of vaccines recommended for children under 9 months of age were included. Each unique vaccination administration date recorded in NYSIIS was considered a vaccination visit for the purposes of this study.
The protocol was approved by the NYS Department of Health Institutional Review Board.

**Vaccine Schedule Grouping**

The number of recommended vaccinations of each type is affected by formulation differences, such as with Rotavirus vaccine (RV) and *Haemophilus influenzae* type b vaccine (Hib), and with scheduling age ranges, such as with HepB and inactivated poliovirus vaccine (IPV) (2). In general, by 9 months of age, children following the RVS should have received 2-3 doses of HepB, 2-3 doses of RV, 3 doses of diphtheria/tetanus/acellular pertussis vaccine (DTaP), 2-3 doses of Hib, 3 doses of pneumococcal conjugate vaccine (PCV), and 2-3 doses of inactivated polio vaccine (IPV) at 3 scheduled visits (24). According to the RVS, therefore, children would receive between four and six vaccines at the first two visits, and at least two vaccines at the third visit.

For this analysis, vaccination coverage was considered separately for each vaccine type that is available in a single disease-specific formulation (i.e., HepB, RV, Hib, PCV, and IPV) and for DTaP, which prevents three diseases but is not available in single disease-specific form. The number of vaccines received was the total of these vaccine types administered (e.g., DTaP-Hib-IPV was considered three vaccines; Hib-HepB was considered two vaccines).

Children were considered to be following the RVS if they had a minimum of three vaccination visits and received five or more vaccinations at two or more of those visits.
Children who had more than three vaccination visits were considered to be following the RVS despite their possible over-vaccination.

Children who did not meet the RVS definition were classified into one of three IDVS patterns 1) restrictive schedule (four or fewer vaccines were administered at all vaccination visits); 2) selective schedule (at least one RVS vaccine was selectively omitted at all vaccination visits); and 3) restrictive and selective schedule (four or fewer vaccines were administered at all vaccination visits and at least one RVS vaccine was selectively omitted).

The age at vaccination visit and spacing between vaccination visits was not assessed as part of the vaccination schedule definitions as it was difficult to determine the reason for vaccination date variability (e.g., parental choice or child illness).

Children who did not fit either the RVS or one of the IDVS definitions were classified as “unknown vaccination schedule.” These children were included in all analyses to produce the most conservative estimates of IDVS.

Assessment of Up-To-Date Status

Age at first vaccination visit, defined as the first visit after 41 days of life or the first visit with a vaccination other than HepB, and the number of vaccination visits from the first visit to 9 months of life were assessed for all children in the study (N= 273,886). Given the complexities of the recommended schedule, children were considered up-to-date (UTD) at nine months if they had received the minimum number of vaccine doses on the RVS from 2 to 6 months: 1 HepB, 2 RV, 3 DTaP, 2 Hib, 3 PCV, and 2 IPV. Only one dose of HepB was considered UTD as the birth dose was removed from analysis.
Children were considered UTD for RV and Hib with two doses because the formulation of these vaccines could not be determined.

**Statistical Analyses**

The proportion of children in each vaccination schedule group (RVS, IDVS, unknown) and the proportion of children using an IDVS in selective, restrictive, and restrictive-selective groups were calculated. The proportion of children considered UTD at nine months and age at first vaccination visit were compared by vaccination schedule group using chi-square tests ($\alpha = 0.05$). The number of vaccination visits and the time from the first vaccination visit to UTD were compared among the vaccination schedule groups using two-sided ANOVA tests or equivalent non-parametric tests where appropriate ($\alpha = 0.05$). County-specific percents of children following an IDVS were calculated. All analyses were completed using SAS 9.2 (SAS Institute, Inc, Cary, NC).

**RESULTS**

**Study Population**

A total of 337,945 children born between January 1, 2009 and August 14, 2011 had vaccines recorded in NYSIIS. Of those, 273,886 children (81%) were eligible for inclusion in this study and categorized into vaccination schedule groups (Table 1). Just over half (57%, N=154,579) of the children were classified as following the RVS. The majority of these children had 3 visits with 5 or more vaccines administered at each visit (72%, N=111,898). Almost one-fourth (24%, N=66,347) of children were classified as following an IDVS. Of these children, most followed a restrictive-selective schedule (43%, N=28,181); almost one-third followed a restrictive-only schedule (31%,
N=20,686); and over one-fourth followed a selective-only schedule (26%, N=17,480).
Approximately 19% (N=52,960) of children did not meet the definition for RVS or IDVS and were classified as unknown vaccination schedule.

Comparison of RVS and IDVS Vaccination Characteristics

There were more IDVS children (13%) with the first vaccination visit recorded at 90 days or older compared with the children following the RVS (2%) (p<0.05). Almost 40% of children following an IDVS schedule had 5 or more vaccination visits before 9 months of age (Table 2).

Among IDVS children following the selective or restrictive-selective schedules (n = 45,661), the two vaccines most commonly omitted were RV (36,035, 79%) and HepB (11,162, 25%). Lack of receipt of HepB, PCV, IPV, HIB and DTaP vaccinations was higher among the restrictive-selective group of children (33%, 21%, 20%, 14%, and 10% respectively) compared to selective-only children (13%, 6%, 0%,1%, and 0% respectively) (p<0.05) (Table 3).

County-level proportions of children following an IDVS ranged from 6% to 67% (median 19%). There was some geographic clustering of higher proportions of IDVS among children in suburban counties around NYC and in rural counties along the Pennsylvania and Canadian borders (Figure 1).

Up-To-Date Status at Nine Months

Children following the RVS were almost seven times as likely to be UTD compared to children following an IDVS (Relative Risk 6.98, 95% CI 6.84, 7.12) (Table
4). By definition none of the children using a selective or restrictive-selective IDVS were UTD for the vaccine series at nine months. Children following a selective schedule were more likely to be UTD for an individual vaccine compared to children following a restrictive-selective schedule (Table 4). Children following any IDVS were less likely to be UTD for the pertussis containing vaccine, DTaP (67%) compared to children attempting to follow the RVS (98%), although only 4% (2,792/67,863) of children following an IDVS did not receive this vaccine (Table 4). Among children attempting to follow the RVS, 90% or more were UTD for each individual vaccine. Among UTD children, those following an IDVS took longer to reach UTD status than RVS children (175 days versus 128 days, p<0.05). (Table 4)

**DISCUSSION**

The success of childhood vaccination programs in preventing disease is dependent on continued efforts to assure that all children are UTD according to the RVS. A substantial proportion (24%) of children under 9 months of age in NYS, outside NYC, currently are not vaccinated according to the RVS. This is concerning, may threaten herd immunity, and contribute to risk of vaccine preventable disease outbreaks.

The estimate of IDVS presented here is higher than results from other recent studies \cite{175,215,249}, but presents a conservative estimate among children in NYS given the consistent deviation from the RVS at all vaccination visits. The inconsistency among IDVS vaccination schedules indicates the true “designer” nature of these schedules. Only about 2.4% of children in this study had two or fewer vaccines per visit, a pattern similar to physician published AVSs \cite{228,230}. One physician-published AVS \cite{230} suggests children
have 3 to 4 extra visits to keep them UTD and almost on track with the RVS, however, approximately 60% of IDVS children in this study did not have these extra visits, consequently leading to a significantly lower UTD status at 9 months.

Studies have not evaluated the impact of these individualized changes to the RVS, thus potentially changing the effectiveness of the provided vaccine coverage. Delays or changes in the RVS during the first few vaccination visits also creates a domino effect that makes catch-up difficult, particularly as a child gets older. While physicians may be willing to accommodate IDVS as a middle-ground response to growing vaccine hesitancy, the true impact of these IDVS on the individual and community is largely unknown. Our data suggest IDVSs could be resulting in a significant degradation of vaccination coverage levels among young children.

It has been reported that parents who adopt an IDVS are disproportionately college educated with high socio-economic status, similar to those of vaccine refusers. The widespread use of IDVS in NYS, outside NYC, could indicate that widespread publicity has moved use of these individualized schedules into the more generalized population. In NYS, outside NYC, county-level proportions of children following an IDVS range from 6% to as high as 67% in counties surrounding NYC. However, there are geographic groupings of high IDVS prevalence in rural areas with lower socio-economic status as well.

The limitations of this study include the incomplete reporting of vaccinations to NYSIIS. Some children with apparent delay in vaccinations could have received some vaccinations outside NYS or from a provider that did not report them to NYSIIS.
However, studies in Texas and Connecticut have shown that registries with high levels of provider participation are often as accurate, or more accurate, than medical record review. Vaccines partially provided in another jurisdiction (e.g., NYC, Pennsylvania) would most likely result in an unknown schedule classification. In addition, intent to follow an IDVS can only be inferred from our data; parents were not contacted to verify intent. However, the significant deviation from the RVS with the definition of IDVS used resulted in significant under-vaccination regardless of parental intent. Children not utilizing a clear vaccination pattern were categorized as unknown to minimize misclassification into the IDVS group. Data-entry error is a possibility, however, these errors would likely affect all groups equally.

Previous estimates have defined IDVS (or AVS) differently including: parental indication of being off-schedule, limiting injections to two per visit, or utilizing ICD-9 codes for refusal. While these estimates yield results where 10-13% of children follow an AVS, our study indicates that consistent systematic deviation from the RVS, a hallmark of IDVS use, is much higher. The ability to find consistent deviations from the RVS in the form of selective refusal or reduction in number of vaccines given using a vaccination registry shows the potential for developing methods to further study the widespread nature of IDVS use.

The estimate provided in this analysis is conservative as children with an unknown schedule, some of which are likely using an IDVS, were included in the denominators. Parents who utilize an IDVS generally hold to consistent ideals of reducing vaccines per visit and selectively refusing specific vaccines, however, the implementation of these techniques is widely varied. Thus, while parents who utilize an
IDVS may start vaccinating their children around the same time as the RVS schedule, only 12% of children were UTD by nine months of age. The increased under-vaccination among this group indicates that many children are intentionally being left at risk for re-emerging infections including measles and pertussis \(^{245;287;290}\). In 2012 more than 41,000 cases of pertussis were reported nationally resulting in 18 deaths \(^{245}\), thus highlighting the ability of these diseases to affect even highly vaccinated populations such as that of the United States \(^{181;287}\). The re-emergence of vaccine-preventable diseases \(^{181;245;287;290}\), coupled with increasing proportions of children using an IDVS, may set the stage for more widespread outbreaks of vaccine-preventable diseases.
Table 1. Vaccination schedule followed by children up to 9 months of age, New York State (outside New York City) study cohort 2009-2011.

<table>
<thead>
<tr>
<th>Vaccination Schedule Group</th>
<th>Definition of Group</th>
<th>N</th>
<th>% of Group¹</th>
<th>% of Total²</th>
<th>Average # of Visits³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended Schedule</strong></td>
<td>3 visits where the child received 5 or 6 recommended vaccines (complete visit)</td>
<td>111,898</td>
<td>72.4%</td>
<td>40.9%</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3 visits with 2 complete vaccination visits and 1 incomplete visit</td>
<td>21,316</td>
<td>13.8%</td>
<td>7.8%</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>2 complete vaccination visits and 1 incomplete visit with a 4th “catch up” visit</td>
<td>20,264</td>
<td>13.1%</td>
<td>7.4%</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>3 complete vaccination visits as well as “extra” vaccine visits (over-vaccinated)</td>
<td>1,010</td>
<td>0.7%</td>
<td>0.4%</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>3 visits but Hb or PCV was missed on 1 or 2 visits possibly due to shortage of vaccine</td>
<td>91</td>
<td>0.1%</td>
<td>0.0%</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Alternative Vaccine Schedule</strong></td>
<td>≤ 4 Vaccines at all vaccination visits</td>
<td>20,686</td>
<td>31.2%</td>
<td>7.6%</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>≤ 3 Vaccines at all vaccination visits⁴</td>
<td>9,274</td>
<td>13.9%</td>
<td>3.4%</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>≤ 2 Vaccines at all vaccination visits⁴</td>
<td>1,574</td>
<td>2.4%</td>
<td>0.6%</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>Selective Vaccine Refusals Only</strong></td>
<td>Omitted at least 1 vaccine (e.g., the child did not receive a single dose by 270 days)</td>
<td>17,480</td>
<td>26.4%</td>
<td>6.4%</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Both Restrictive-selective Refusals</strong></td>
<td>≤ 4 Vaccines at all vaccination visits and Omitted at least 1 vaccine</td>
<td>28,181</td>
<td>42.5%</td>
<td>10.3%</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>≤ 3 Vaccines at all vaccination visits and Omitted at least 1 vaccine</td>
<td>15,554</td>
<td>23.4%</td>
<td>5.7%</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>1 or 2 complete visits and then no other recorded visits</td>
<td>52,960</td>
<td>100%</td>
<td>19.3%</td>
<td>2.2⁵</td>
</tr>
<tr>
<td></td>
<td>Any remaining unclassified children</td>
<td>10,340</td>
<td>19.9%</td>
<td>3.8%</td>
<td>4.4</td>
</tr>
</tbody>
</table>

¹Denominator: the overall category. Alternative vaccine schedule (N=66,347), recommended schedule (N=154,579), or Unknown schedule (N=52,960).
²Denominator: all eligible children in the study (N=233,888).
³Average number of visits from the first study visit (i.e., the first visit where a vaccine other than Hepatitis B vaccine was given or the first visit after 41 days of age) through 270 days of age.
⁴Includes children counted previously in the above category.
⁵Number of visits visits significantly by group p < 0.0001
Table 2. **Age at first vaccination visit and number of vaccination visits at 9 months of age by vaccination schedule group, New York State (outside New York City) Study Cohort 2009-2011**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recommended Schedule n=154,579</th>
<th>Alternative Vaccine Schedule n=66,347</th>
<th>Unknown n=52,960</th>
<th>All Children n=273,886</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at First Visit</strong>&lt;sup&gt;a,b&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Months</td>
<td>701 (0.4)</td>
<td>1,132 (1.7)</td>
<td>306 (0.6)</td>
<td>2,139 (0.8)</td>
</tr>
<tr>
<td>(0-41 Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Months</td>
<td>150,201 (97.2)</td>
<td>56,766 (85.6)</td>
<td>37,889 (71.5)</td>
<td>244,856 (89.4)</td>
</tr>
<tr>
<td>(42-89 Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Months</td>
<td>3,640 (2.4)</td>
<td>5,442 (8.2)</td>
<td>10,006 (18.9)</td>
<td>19,088 (7.0)</td>
</tr>
<tr>
<td>(90-149 Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>37 (0.0)</td>
<td>2,064 (3.1)</td>
<td>3,647 (6.9)</td>
<td>5,748 (2.1)</td>
</tr>
<tr>
<td>(150-209 Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8+ Months</td>
<td>0 (0.0)</td>
<td>943 (1.4)</td>
<td>1,112 (2.1)</td>
<td>2,055 (0.8)</td>
</tr>
<tr>
<td>(210-300 Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of Vaccination Visits</strong>&lt;sup&gt;c,d&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 Visits</td>
<td>0 (0.0)</td>
<td>8,838 (13.3)</td>
<td>42,420 (80.1)</td>
<td>51,258 (18.7)</td>
</tr>
<tr>
<td>3 Visits</td>
<td>133,279 (86.2)</td>
<td>22,778 (34.3)</td>
<td>2,972 (5.6)</td>
<td>159,029 (58.1)</td>
</tr>
<tr>
<td>4 Visits</td>
<td>20,275 (13.1)</td>
<td>8,657 (13.1)</td>
<td>2,071 (3.9)</td>
<td>31,003 (11.3)</td>
</tr>
<tr>
<td>5-6 Visits</td>
<td>1,018 (0.7)</td>
<td>20,647 (31.1)</td>
<td>5,289 (10.0)</td>
<td>26,954 (9.8)</td>
</tr>
<tr>
<td>7-9 Visits</td>
<td>7 (0.0)</td>
<td>5,033 (7.6)</td>
<td>208 (0.4)</td>
<td>5,248 (1.9)</td>
</tr>
<tr>
<td>10-16 Visits</td>
<td>0 (0.0)</td>
<td>394 (0.6)</td>
<td>0 (0.0)</td>
<td>394 (0.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>The first vaccination visit at which the child received a vaccine other than Hepatitis B vaccination or the first vaccination visit after 41 days of age.

<sup>b</sup> Age at first visit varies significantly by group chi-square p<0.0001

<sup>c</sup>The number of vaccination visits up to 270 days of age, other than Hepatitis B vaccination only visits before 42 days of age.

<sup>d</sup>Number of vaccination visits varies significantly by group chi-square p<0.0001
Table 3. Vaccines missed/refused among AVS children for the selective only and the restrictive-selective vaccination schedule groups, New York State (outside New York City), Study Cohort 2009-2011.

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Selective Only AVS</th>
<th>Restrictive-selective AVS</th>
<th>All Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>(N = 17,480)</td>
<td>(N = 28,181)</td>
<td>(N = 273,886)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>13,965 (79.9)</td>
<td>22,070 (78.3)</td>
<td>36,035 (13.2)</td>
</tr>
<tr>
<td>Hepatitis B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2,188 (12.5)</td>
<td>9,414 (33.4)</td>
<td>11,602 (4.2)</td>
</tr>
<tr>
<td>Pneumococcal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,093 (6.3)</td>
<td>5,906 (21.0)</td>
<td>6,999 (2.6)</td>
</tr>
<tr>
<td>Polio Virus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57 (0.3)</td>
<td>5,520 (19.6)</td>
<td>5,577 (2.0)</td>
</tr>
<tr>
<td>Haemophilus influenzae type B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>169 (1.0)</td>
<td>3,849 (13.7)</td>
<td>4,018 (1.5)</td>
</tr>
<tr>
<td>Diphtheria, Tetanus, and Pertussis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (0.1)</td>
<td>2,784 (9.9)</td>
<td>2,792 (1.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Indicates that the restrictive-selective group had significantly higher refusal compared to the selective only group chi-square p<0.05
Table 4. Number of days from first vaccination visit to visit at which children 9 months of age become up-to-date \(^a\) New York State (outside New York City) Study Cohort 2009-2011.

<table>
<thead>
<tr>
<th>Vaccination Schedule Group</th>
<th>Number in Group</th>
<th>Up to date (UTD)(^a)</th>
<th>Days from two month visit to UTD(^b)</th>
<th>HepB UTD</th>
<th>RV UTD</th>
<th>DTaP UTD</th>
<th>Hib UTD</th>
<th>PCV UTD</th>
<th>IPV UTD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended Schedule</strong></td>
<td>154,579</td>
<td>138,897 (89.9)</td>
<td>128 (102-203)</td>
<td>154,579</td>
<td>152,335 (98.6)</td>
<td>150,842</td>
<td>154,202 (99.8)</td>
<td>142,792</td>
<td>154,534 (100)</td>
</tr>
<tr>
<td><strong>Alternative Vaccine Schedule</strong></td>
<td>66,347</td>
<td>8,388 (12.6)</td>
<td>175 (119-223)</td>
<td>54,745</td>
<td>26,255 (39.6)</td>
<td>44,595</td>
<td>54,769 (82.6)</td>
<td>34,062</td>
<td>51,461 (77.6)</td>
</tr>
<tr>
<td><strong>Restrictive(^b)</strong></td>
<td>20,686</td>
<td>8,388 (40.6)</td>
<td>175 (119-223)</td>
<td>20,686</td>
<td>18,770 (90.7)</td>
<td>14,756</td>
<td>19,099 (92.3)</td>
<td>10,768</td>
<td>17,427 (84.3)</td>
</tr>
<tr>
<td><strong>Selective(^c)</strong></td>
<td>28,466</td>
<td>0 (0.0)</td>
<td>N/A</td>
<td>23,581</td>
<td>4,892 (17.2)</td>
<td>16,386</td>
<td>22,796 (80.1)</td>
<td>14,501</td>
<td>23,018 (80.6)</td>
</tr>
<tr>
<td><strong>Restrictive and Selective(^d)</strong></td>
<td>28,181</td>
<td>0 (0.0)</td>
<td>N/A</td>
<td>18,767</td>
<td>4,064 (14.4)</td>
<td>13,253</td>
<td>18,489 (65.6)</td>
<td>8,793</td>
<td>16,741 (59.4)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>52,060</td>
<td>5,092 (9.6)</td>
<td>160 (108-222)</td>
<td>50,263</td>
<td>28,926 (54.6)</td>
<td>8,253</td>
<td>36,730 (69.4)</td>
<td>6,688</td>
<td>37,528 (70.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>273,886</td>
<td>152,377 (55.6)</td>
<td>130 (102-208)</td>
<td>259,587</td>
<td>207,516 (75.8)</td>
<td>203,690</td>
<td>245,701 (89.7)</td>
<td>183,542</td>
<td>243,523 (88.9)</td>
</tr>
</tbody>
</table>

Abbreviations: AVS, Alternative Vaccination Schedule; UTD, up to date; HepB, Hepatitis B vaccine; RV, Rotavirus vaccine; DTaP, Diphtheria, Tetanus, and Pertussis vaccine; Hib, Haemophilus influenzae vaccine; PCV, Pneumococcal conjugate vaccine.

\(^a\) Up-to-date = 1 HepB, 3 IPV, 3 DTaP, 2 Hib, 3 PCV, 2 IPV
\(^b\) = 4 vaccines at all vaccination visits
\(^c\) Refused at least 1 vaccine entirely (e.g., the child did not receive a single dose by 270 days)
\(^d\) = 4 vaccines at all vaccination visits and refused at least 1 vaccine entirely
\(^e\) Range is from 1% to 99% to exclude extreme values
\(^f\) ANOVA analysis indicates all groups are statistically different (p<0.05)
Figure 1. Proportion\(^a\) of children following an Individually Designed Vaccination Schedule (IDVS) by County, in New York State, outside New York City

The proportion of children in the New York State Immunization Information System (NYSIIS) following an IDVS through nine months of age by county. Proportions range from 6\% to 67\%.

\(^a\) The denominator includes children following an unknown schedule.
Abstract

**Background:** Despite research showing the safety and efficacy of the current recommended vaccination schedule, between 10% and 24% of children in the United States are vaccinated following an alternative vaccination schedule (AVS). Intentional deviation from the recommended vaccination schedule has been shown to increase a child’s risk for developing and spreading vaccine preventable diseases.

**Methods:** Children with vaccination records in the New York State Immunization Information System were classified as to whether or not they were vaccinated with patterns consistent with use of an alternative vaccination schedule. Vaccination schedule information was linked with zip-code level census based data. Log binomial and Poisson regression analysis were used to determine risk factors for increased use of AVS in communities.

**Results:** The proportion of children in each birth cohort following an AVS decreased by 4% from 2009 to 2011 (25.6% to 21.4% respectively). Vaccination following an AVS was most significantly correlated with median household income \( r=0.46, p<0.0001 \) and increased education \( r=0.38, p<0.0001 \). Multivariate regression showed communities with a median household income over $75,000 or more were more likely than communities with median household incomes of under $30,000 to have increased rates of AVS \( (RR \ 3.16, \ 95\%CI \ 2.90-3.44) \).
Conclusions: The proportion of children vaccinated following an AVS in New York State, outside New York City, remains over 20% despite decreases between children born in 2009 and children born in 2011. Increased proportions of AVS were seen in communities with increased median household incomes and higher education.
INTRODUCTION

The use of alternative vaccination schedules (AVS) has been shown to leave children under-immunized and thus vulnerable to infection by vaccine preventable diseases (VPD)\(^{246;247;249;280}\). The proportion of children vaccinated following an AVS in the United States ranges between 10 and 24% and has been shown to be increasing over time leaving larger numbers of children vulnerable to preventable diseases\(^{175;188;211;215;249}\). Parents choose to use an AVS for a number of reasons including concern over the safety and efficacy of vaccines, a belief that children receive too many vaccines too soon, miss-understanding contraindications to vaccination, and the belief that their child is not at risk for VPD\(^{178;188;190;211;215;278}\). Children following and AVS have also been shown to utilize less health care, frequent alternative medicine providers, and live in white households with higher incomes, more children, and private insurance\(^{215;249;280}\).

Published AVS give an air of legitimacy to AVS, and suggest vaccine hesitant parents hide in the herd, relying on the civic duty of other parents to protect their own children\(^{228;230;233}\). Increasing vaccine refusal and under-immunization leaves children unprotected thus leading to outbreaks of VPD including measles, mumps, and pertussis\(^{181;241;246;280}\). Researchers warn that under-vaccination due to intentional delay or refusal of vaccines has the potential to increase by up to 40%\(^{188;189;213;215}\). Currently, discussions with a physician are swaying vaccine hesitant parents towards vaccination\(^{187-189}\), however, more recent studies indicate that physicians, particularly younger physicians, are increasingly willing to administer AVS upon parental request\(^{197;291}\). A small proportion of physicians even administer an AVS in the absence of parental request\(^{197}\).
While the demographic and socioeconomic status of unvaccinated children, vaccine hesitant parents, and children whose parents self-report following an AVS have been described, to date no study has linked sociodemographic characteristics with children documented to be following an AVS through review of immunization history. The increasing use of AVS throughout the country highlights the need to better understand characteristics of parents and physicians who request and administer these schedules. This study utilizes immunization histories obtained through the New York State Immunization Information System and community level demographic and socioeconomic information to determine characteristics associated with increased use of AVS.

METHODS

The New York State Immunization Information System (NYSIIS) is a statewide immunization registry containing information on immunizations administered to residents of New York State (NYS), outside New York City (NYC). Mandatory reporting of immunization information for children age 19 and younger began in 2008. By 2011 it was estimated that 90% of physicians were reporting to NYSIIS which covered 88% of children 6 years of age and younger in NYS, outside NYC. Immunization records for children born between January 1, 2009 and August 14, 2011 were obtained from NYSIIS on May 12, 2012.

The Advisory Committee on Immunization Practices (ACIP) recommends that between two and six months of age children receive two doses of Hepatitis B vaccine (HepB), three doses of Diphtheria, Tetanus, and Pertussis vaccine (DTaP), three doses of
inactivated polio vaccine (IPV), two or three doses of *Haemophilus influenzae* type b vaccine (Hib), three doses of Pneumococcal conjugate vaccine (PCV), and two or three doses of Rotavirus vaccine (RV). These vaccines are given over three well child visits scheduled at two, four and six months of age, with a child generally receiving between five and six vaccines at each visit.

Immunization visits between 42 days (the earliest age a child is eligible for the 2 month vaccination visit) and 270 days (9 months) of age were assessed for two common patterns consistent with the use of an AVS: 1) reducing the number of individual vaccines from six to four or fewer at all unique vaccination dates and 2) having no doses recorded of at least one of the six recommended vaccinations. Children who met one or both of these criteria were classified as following an AVS.

For each child with vaccinations recorded in NYSIIS, additional limited demographic information is also available including: gender, date of birth, as well as zip code and county of residence. Each vaccination recorded also has a unique identifier for the practice reporting the vaccination and the zip code of the practice location. The number of practices reporting vaccinations for each child was determined and classified as one practice or multiple practices. The practice reporting the most unique vaccination dates, or the last practice seen in the event of a tie, was considered the primary practice for each child. The distance between the centroid of the zip code of residence listed for the child and the zip code of the primary practice location was calculated as an estimate of the distance traveled to provider.
To obtain additional demographic information on race, ethnicity, and socioeconomic status zip code level information is obtained for NYS zip codes from the American Community Survey (ACS) 5 year averages from 2007 to 2011. The ACS provides demographic and economic information at the zip code population level including: median household income, poverty rate, GINI income coefficient (a measure of income inequality), percent of persons over 16 who are unemployed, the percent of persons over 25 with a bachelor’s degree or higher, the percent of households reporting children under 18, and the percent of residents who are white non-Hispanic, black non-Hispanic, Asian, or Hispanic. Demographic and socioeconomic variables obtained from the ACS were classified into groups based on previous literature and size considerations.

To obtain information on the urbanicity of each zip code in NYS Rural-Urban Commuting Area (RUCA) codes were obtained from the United States Department of Agriculture Economic Research Service. Rural-urban commuting area codes were classified as urban (codes < 3), suburban (codes 3 -<7), and rural (codes 7+).

The association between individual demographic characteristics provided in NYSIIS (e.g. gender, year of birth, number of providers, approximated distance traveled to provider) and vaccination following an AVS was determined using Log binomial regression to calculate unadjusted risk ratios. Adjusted risk ratios for the association between individual characteristics and vaccination following an AVS were also calculated with all individual level variables in a multivariable log binomial regression model, this model was adjusted for clustering in communities.

To better understand the association between demographic and socioeconomic characteristics not available through NYSIIS and vaccination following an AVS, children
were matched to ACS and RUCA data based on their zip code of residence. The number of children vaccinated following an AVS in a zip code was modeled using Poisson regression analysis. Unadjusted and adjusted rate ratios were determined for median household income, poverty rate, GINI income coefficient, unemployment, education, race and ethnicity, and urbanicity variables. Spearman correlation coefficients were calculated between the proportion of children following an AVS in each zip code and all zip code level variables. All analysis was conducted utilizing SAS 9.3 (SAS institutes, Cary, NC) with an alpha of 0.05.

This study was approved by the authors institutional review board.

RESULTS

As of May 12, 2012, a total of 273,886 children born between January 1, 2009 and August 14, 2011 residing in NYS, outside NYC, had vaccinations recorded in NYSIIS between 42 and 270 days of age. Of those children 270,816 (98.9%) were linked by zip code to socioeconomic and demographic data. The children who were not linked had either a zip code that did not link to ACS data (eg, nonresidential zip code) or no zip code listed in NYSIIS.

Almost one-fourth (24.2%, N=65,653) of children were classified as following an AVS. These children were distributed throughout NYS, the proportion of children following an AVS in each zip code ranged from 0% to 96% (mean=25.0, median 19.0).

The proportion of children following an AVS was generally similar across all individual characteristics (Table 1). The proportion of children vaccinated following an AVS was 4% greater for children born in 2009 compared to children born in 2011 (25.5%
and 21.4% respectively, p<0.0001). Gender, number of providers, and distance to provider had little to no effect on the risk of following an AVS (Table 1).

The rate of AVS in a zip code was positively associated with increases in median household income (r = 0.46, p<0.0001), education (r = 0.38, p<0.0001), proportions of Asian residents (r = 0.22, p<0.0001), and proportions of Hispanic residents (r=0.15, <0.0001). Conversely, the rate of AVS in a zip code was negatively associated with increasing poverty (r = -0.26, p<0.0001), unemployment (r = -0.09, p<0.0001), and proportions of black/African American residents (r = -0.10, p<0.0001) (Table 2). Adjusting for all community level socioeconomic and demographic variables urban and suburban zip codes also had lower rates of AVS compared to rural zip codes (RR0.62, 95%CI 0.60-0.64 and RR 0.78, 95%CI 0.70-0.84 respectively) (Table 2).

DISCUSSION

Communities with greater incomes and education had statistically higher rates of children vaccinated following an AVS. While this paper was unable to assess income and education among families of AVS children, the consistency among all income related variables indicates that these factors may indeed be strong predictors of AVS use. These neighborhood findings are consistent with those of other studies which found that parents who report utilizing an AVS had higher incomes and education \(^{215,247}\). The same is true of parents who refuse some or all vaccinations \(^{178,180}\). This study also shows that communities with larger proportions of black/African American residents had lower rates of AVS. Studies of both AVS and vaccine exemption have also found lower rates in non-white persons \(^{178,180,215,247}\).
Surprisingly the proportion of children vaccinated following an AVS decreased from 2009 to 2011 where as other studies have indicated that the proportion of AVS is increasing over time. This decrease may in part be due to increases in rotavirus uptake. A previous study of AVS in NYS found that 13% of children vaccinated following an AVS did not receive RV. If RV is removed from analysis the decrease between 2009 and 2011 is significantly reduced but not eliminated suggesting other factors may also be playing a role (data not shown). Parents, physicians, and nurses have been shown to be more accepting of vaccinations that require fewer injections. While this study did not assess vaccine brand use, a study of shot limiting behavior in Oregon found that the use of Pentacel, a combination vaccine that reduces the number of injections needed to 3 or less, has been increasing. Reducing the number of physical injections needed through the use of combination vaccines may assuage some vaccine hesitant parents who are more concerned with the emotional distress, both for baby and parent, of multiple injections at one visit.

This study found associations between Hispanicity and Asian race that were not previously found in other studies. The majority of NYS zip codes consist of 90% or more non-Hispanic white residents. Zip codes with higher proportions of Hispanic and Asian residents are predominantly Urban suggesting that income is a stronger risk factor for high rates of AVS than race/ethnicity in these areas. These results could also suggest that increased rates of AVS have moved into communities other than wealthy, educated, white communities.

While the findings of this study are largely consistent with other studies of AVS use and vaccine refusal this study has several limitations. While NYS law mandates the
reporting of childhood immunizations to NYSIIS the accuracy of this data can be affected by data entry errors, including both keystroke errors and systematic errors, and lack of reporting. Staff at the NYS Department of Health train providers to use NYSIIS and ensure that uploaded data from electronic medical records is accurate, thus reducing systematic error. Also this study could be subject to the ecologic fallacy since most socioeconomic and demographic covariates were measured at the zip-code level. The use of census-based data to understand community based risk factors for individual outcomes has been previously used. These results are also consistent with other studies using both census-based and individual level data; however, care should be exercised when generalizing the results of this study to individual children. This study also used a narrow definition of AVS, reduction in vaccines given at all visits or refusal of at least one vaccine, thus other characteristics of AVS such as delay in start of vaccination or different patterns would be in the denominator, potentially reducing the effects seen in this study.

CONCLUSIONS

This is the first study to determine characteristics associated with higher rates of AVS in a community setting by utilizing a child’s vaccination record rather than parental self-report. Communities with higher rates of AVS a disproportionately have higher median incomes, increased levels of education, and lower proportions of black/African American residents.
Table 1. Demographic characteristics of children following an alternative vaccination schedule in New York State, outside New York City

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule Users N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>132,658 (49.0)</td>
<td>31,883 (24.0)</td>
<td>Referent</td>
<td>Referent</td>
<td>1.01</td>
<td>(1.01-1.02)</td>
</tr>
<tr>
<td>Male</td>
<td>137,913 (51.0)</td>
<td>33,699 (24.4)</td>
<td></td>
<td></td>
<td>1.01</td>
<td>(1.00-1.01)</td>
</tr>
<tr>
<td>Year of Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>108,264 (40.0)</td>
<td>27,758 (25.6)</td>
<td>Referent</td>
<td>Referent</td>
<td>1.0</td>
<td>(0.98-1.01)</td>
</tr>
<tr>
<td>2010</td>
<td>102,758 (37.9)</td>
<td>25,120 (24.5)</td>
<td>1.00</td>
<td>(0.97-1.03)</td>
<td>1.00</td>
<td>(1.00-1.01)</td>
</tr>
<tr>
<td>2011</td>
<td>59,794 (22.1)</td>
<td>12,775 (21.4)</td>
<td>0.85</td>
<td>(0.84-0.87)</td>
<td>0.85</td>
<td>(0.84-0.87)</td>
</tr>
<tr>
<td>Number of Providers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>249,036 (92.0)</td>
<td>60,368 (24.2)</td>
<td>Referent</td>
<td>Referent</td>
<td>1.00</td>
<td>(0.97-1.03)</td>
</tr>
<tr>
<td>2-4</td>
<td>21,780 (8.0)</td>
<td>5,285 (24.3)</td>
<td>1.00</td>
<td>(0.97-1.03)</td>
<td>1.00</td>
<td>(0.99-1.01)</td>
</tr>
<tr>
<td>Distance to Provider</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>68,086 (25.1)</td>
<td>15,655 (23.0)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-&lt;10 miles</td>
<td>141,529 (52.3)</td>
<td>35,229 (24.9)</td>
<td>1.08</td>
<td>(1.06-1.10)</td>
<td>1.08</td>
<td>(1.06-1.10)</td>
</tr>
<tr>
<td>10-&lt;25 miles</td>
<td>51,006 (18.8)</td>
<td>12,220 (24.0)</td>
<td>1.04</td>
<td>(1.02-1.06)</td>
<td>1.04</td>
<td>(1.02-1.06)</td>
</tr>
<tr>
<td>25-&lt;50 miles</td>
<td>7,711 (2.9)</td>
<td>1,992 (25.8)</td>
<td>1.12</td>
<td>(1.07-1.17)</td>
<td>1.12</td>
<td>(1.07-1.16)</td>
</tr>
<tr>
<td>50+ miles</td>
<td>2,473 (0.9)</td>
<td>548 (22.2)</td>
<td>0.96</td>
<td>(0.89-1.04)</td>
<td>0.95</td>
<td>(0.88-1.03)</td>
</tr>
</tbody>
</table>

<sup>a.</sup> Risk Ratio was calculated using log binomial regression analysis

<sup>b.</sup> Adjusted risk ratios were calculated using log binomial regression adjusting for gender, year of birth, number of providers, distance to provider
Table 2. Community based demographic and socioeconomic characteristics associated with increased rates of children vaccinated following an alternative vaccination schedule in New York State, outside New York City

<table>
<thead>
<tr>
<th>Urbanicity</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt; 95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; 95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>22,153 (8.2)</td>
<td>5,177 (23.4)</td>
<td>340 (26.0)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Suburban</td>
<td>28,050 (10.4)</td>
<td>4,772 (17.0)</td>
<td>787 (60.1)</td>
<td>0.73 (0.70-0.76)</td>
<td>0.78 (0.75-0.82)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>220,613 (81.5)</td>
<td>55,704 (25.3)</td>
<td>183 (13.9)</td>
<td>1.08 (1.05-1.11)</td>
<td>0.61 (0.60-0.64)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Household Income</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt; 95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; 95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than $30,000</td>
<td>13,718 (5.1)</td>
<td>938 (6.8)</td>
<td>39 (3.0)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>$30,000 - &lt;$50,000</td>
<td>85,366 (31.5)</td>
<td>13,799 (16.2)</td>
<td>476 (36.3)</td>
<td>2.36 (2.22-2.52)</td>
<td>1.92 (1.77-2.07)</td>
<td></td>
</tr>
<tr>
<td>$50,000 - &lt;$75,000</td>
<td>91,367 (33.7)</td>
<td>18,702 (20.5)</td>
<td>487 (37.2)</td>
<td>2.99 (2.81-3.19)</td>
<td>2.32 (2.14-2.51)</td>
<td></td>
</tr>
<tr>
<td>$75,000 +</td>
<td>80,365 (29.7)</td>
<td>32,214 (40.1)</td>
<td>308 (23.5)</td>
<td>5.86 (5.51–6.24)</td>
<td>3.16 (2.90-3.44)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poverty Rate</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt; 95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; 95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5%</td>
<td>62,885 (23.2)</td>
<td>24,264 (38.6)</td>
<td>319 (24.4)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>5% - &lt;10%</td>
<td>72,331 (26.7)</td>
<td>17,798 (24.6)</td>
<td>380 (29.0)</td>
<td>0.64 (0.63-0.65)</td>
<td>0.84 (0.82-0.87)</td>
<td></td>
</tr>
<tr>
<td>10% - &lt;15%</td>
<td>47,337 (17.5)</td>
<td>9,082 (19.2)</td>
<td>285 (21.8)</td>
<td>0.50 (0.49–0.51)</td>
<td>0.86 (0.83-0.89)</td>
<td></td>
</tr>
<tr>
<td>15% - &lt;20%</td>
<td>35,827 (13.2)</td>
<td>6,573 (18.4)</td>
<td>179 (13.7)</td>
<td>0.48 (0.46-0.49)</td>
<td>0.80 (0.77-0.83)</td>
<td></td>
</tr>
<tr>
<td>20% +</td>
<td>52,436 (19.4)</td>
<td>7,936 (15.1)</td>
<td>147 (11.2)</td>
<td>0.39 (0.38-0.40)</td>
<td>0.78 (0.74-0.81)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GINI Income Coefficient</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt; 95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; 95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 0.4</td>
<td>101,523 (37.5)</td>
<td>26,419 (26.0)</td>
<td>692 (52.8)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>0.4 - &lt;0.45</td>
<td>96,508 (35.6)</td>
<td>21,559 (22.3)</td>
<td>380 (29.0)</td>
<td>0.86 (0.85-0.87)</td>
<td>1.09 (1.07-1.12)</td>
<td></td>
</tr>
<tr>
<td>0.45 +</td>
<td>72,785 (26.9)</td>
<td>17,675 (24.3)</td>
<td>238 (18.2)</td>
<td>0.93 (0.92-0.95)</td>
<td>1.21 (1.18-1.24)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent Unemployed</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt; 95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; 95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5%</td>
<td>46,744 (17.3)</td>
<td>12,985 (27.8)</td>
<td>349 (26.6)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>5% - &lt;10%</td>
<td>178,292 (65.8)</td>
<td>46,286 (26.0)</td>
<td>715 (54.6)</td>
<td>0.93 (0.92-0.95)</td>
<td>1.04 (1.02-1.06)</td>
<td></td>
</tr>
<tr>
<td>10% +</td>
<td>45,775 (16.9)</td>
<td>6,380 (13.9)</td>
<td>246 (18.8)</td>
<td>0.50 (0.49-0.52)</td>
<td>0.87 (0.84-0.90)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent of Persons over 25 years with a Bachelor's degree or greater</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt; 95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; 95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 15%</td>
<td>35,139 (13.0)</td>
<td>4,920 (14.0)</td>
<td>298 (22.8)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>15% - &lt;30%</td>
<td>125,980 (46.5)</td>
<td>25,135 (20.0)</td>
<td>570 (43.5)</td>
<td>1.42 (1.38-1.46)</td>
<td>1.15 (1.11-1.18)</td>
<td></td>
</tr>
<tr>
<td>30% +</td>
<td>109,697 (40.5)</td>
<td>35,598 (32.5)</td>
<td>442 (33.7)</td>
<td>2.30 (2.24-2.37)</td>
<td>1.35 (1.29-1.40)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Rate ratio was calculated using Poisson regression analysis
<sup>b</sup> Adjusted rate ratios were calculated using Poisson regression adjusting for all other community level covariates in the model
Table 2 continued. Community based demographic and socioeconomic characteristics associated with increased rates of children vaccinated following an alternative vaccination schedule in New York State, outside New York City

<table>
<thead>
<tr>
<th>Percent White</th>
<th>Number of Children N(%)</th>
<th>Alternative Vaccine Schedule N (%)</th>
<th>Number of Zip Codes N (%)</th>
<th>Crude RR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI</th>
<th>Spearmans Coefficient (Pvalue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 25%</td>
<td>46,940 (17.3)</td>
<td>9,462 (20.2)</td>
<td>70 (5.3)</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25% - &lt;35%</td>
<td>52,396 (19.4)</td>
<td>13,615 (26.0)</td>
<td>145 (11.1)</td>
<td>1.29</td>
<td>(1.26-1.32)</td>
<td>1.08</td>
<td>(1.04-1.13)</td>
<td></td>
</tr>
<tr>
<td>35% - &lt;45%</td>
<td>79,706 (29.4)</td>
<td>24,012 (30.1)</td>
<td>304 (23.2)</td>
<td>1.49</td>
<td>(1.46-1.53)</td>
<td>1.20</td>
<td>(1.14-1.26)</td>
<td></td>
</tr>
<tr>
<td>45% +</td>
<td>91,774 (33.9)</td>
<td>18,564 (20.2)</td>
<td>791 (60.4)</td>
<td>1.00</td>
<td>(0.98-1.03)</td>
<td>1.17</td>
<td>(1.11-1.25)</td>
<td></td>
</tr>
</tbody>
</table>
| Percent Black | -0.04 (0.18)             |                                   |                           |                      |       |                          |       |-
| Less than 1%  | 61,177 (22.6)            | 16,000 (26.2)                     | 673 (51.4)                | Referent             | Referent |
| 1% - <10%     | 131,227 (48.5)           | 34,338 (26.2)                     | 484 (37.0)                | 1.0                  | (0.98-1.02) | 0.87                 | (0.85-0.89) |
| 10% - <20%    | 33,599 (12.4)            | 7,514 (22.4)                      | 81 (6.2)                  | 0.86                 | (0.83-0.88) | 0.88                 | (0.85-0.92) |
| 20% +         | 44,813 (16.6)            | 7,801 (17.4)                      | 72 (5.5)                  | 0.67                 | (0.65-0.68) | 0.82                 | (0.78-0.87) |
| Percent Asian | 0.22 (<.0001)            |                                   |                           |                      |       |                          |       |-
| Less than 1%  | 81,730 (30.2)            | 15,345 (18.8)                     | 754 (57.6)                | Referent             | Referent |
| 1% - <10%     | 137,425 (50.7)           | 33,466 (24.4)                     | 410 (31.3)                | 1.30                 | (1.28-1.32) | 1.10                 | (1.07-1.14) |
| 10% +         | 51,661 (19.1)            | 16,842 (32.6)                     | 146 (11.1)                | 1.74                 | (1.70-1.77) | 1.21                 | (1.17-1.26) |
| Percent Hispanic | 0.15 (<.0001)          |                                   |                           |                      |       |                          |       |-
| Less than 1%  | 20,537 (7.6)             | 4,008 (19.5)                      | 360 (27.5)                | Referent             | Referent |
| 1% - <5%      | 110,672 (40.9)           | 20,459 (18.5)                     | 533 (40.7)                | 0.94                 | (0.91-0.97) | 0.93                 | (0.90-0.97) |
| 5% - <15%     | 80,641 (29.8)            | 25,814 (32.0)                     | 304 (23.2)                | 1.63                 | (1.59-1.68) | 1.47                 | (1.41-1.54) |
| 15% +         | 58,966 (27.8)            | 15,372 (26.1)                     | 113 (8.6)                 | 1.33                 | (1.29-1.37) | 1.56                 | (1.48-1.64) |
| Percent of Households With Kids | 0.12 (<.0001) |                                   |                           |                      |       |                          |       |-
| Less than 25% | 24,685 (9.1)             | 4,659 (18.9)                      | 219 (16.7)                | Referent             | Referent |
| 25% - <35%    | 132,255 (48.8)           | 25,215 (19.1)                     | 612 (46.7)                | 1.01                 | (0.98-1.03) | 0.98                 | (0.95-1.01) |
| 35% - <45%    | 94,728 (35.0)            | 30,133 (31.8)                     | 388 (29.6)                | 1.69                 | (1.64-1.73) | 1.22                 | (1.18-1.27) |
| 45% +         | 19,148 (7.1)             | 5,646 (29.5)                      | 91 (7.0)                  | 1.65                 | (1.51-1.62) | 1.37                 | (1.31-1.43) |

- a. Rate ratio was calculated using Poisson regression analysis
- b. Adjusted rate ratios were calculated using Poisson regression adjusting for all other community level covariates in the model
**Paper 3 - Reporting of Alternative Vaccine Schedule use at Medical Practices in New York State**

**Abstract**

*Background:* Alternative vaccination schedules (AVS) may lead to pockets of under-vaccination and thus increase the spread of vaccine preventable diseases in certain communities. This study identifies the characteristics of medical practices serving children age 2 to 9 months vaccinated following patterns consistent with AVS.

*Methods:* Children with vaccinations recorded in the New York State Immunization Information System were classified by type of vaccination schedule: the recommended vaccination schedule (RVS), an alternative vaccination schedule (AVS), or an unknown vaccination schedule. The proportion of children in a practice following each vaccination schedule and the proportion receiving at least one dose of each recommended vaccine is reported by size (number of pediatric patients), type (private practice, health department clinic, etc.), and location of the practice (urban, suburban, rural).

*Results:* Practices with 1000 or more children reported the highest proportion of children following the RVS (77.9%) while practices with 10 to 99 children reported the highest proportion of children following an AVS (25.8%). Practices in suburban counties reported the highest proportion of children following the RVS (60.7%) while practices in urban counties reported the highest number of children following an AVS (20.0%). Federally qualified health centers had the highest proportion of children following the RVS (64.6%) and the lowest proportion of children following an AVS (6.1%). The
lowest proportions of children receiving vaccines were for rotavirus vaccine, small practices (82.0%) and rural practices (80.6%) had the lowest proportion of children receiving rotavirus vaccine.

Conclusions: The proportion of children following an AVS in a practice is significantly associated with the size and location of the practice. While high proportions of children received most vaccines, rotavirus vaccine had the lowest proportion of children receiving vaccine.
INTRODUCTION

Younger physicians and new parents may have increased concern about the safety and efficacy of both individual childhood vaccines and the current Advisory Committee on Immunization Practices (ACIP) recommended childhood vaccination schedule (RVS) 180;189;291. “Vaccine-hesitant” parents may ask physicians to deviate from the RVS by refusing individual vaccines, delaying vaccination, or spreading vaccines out over longer intervals. These variations from the RVS are commonly referred to as alternative vaccination schedules (AVS) 175;215;249. The use of an AVS may cause children not to be up-to-date in their vaccinations 175;188;249 which is associated with increased risk of vaccine preventable disease for both individuals and communities 184;246;280. It is currently estimated that between 10% and 24% of US children are being vaccinated on an AVS. While AVS vary considerably in definition and prevalence 175;188;215;249, a recent national survey found that in a typical month an estimated 79% of physicians reported at least one vaccine refusal and 89% of physicians reported at least one request to delay one or more vaccines 189.

Pediatric health care providers are in a sometimes difficult position of promoting the importance of childhood vaccinations against a backdrop of increased parental concern about vaccines. Physicians remain the most trusted source of information regarding childhood vaccination 187. Many parents agree to have their children vaccinated despite concerns after consultation with their physician. One study indicated that almost 40% of parents who plan to delay or refuse vaccination change their minds after a discussion with their physician 188. A small but increasing number of physicians have concerns regarding the safety and necessity of vaccines 187;188;197;201;211;291;293 eight percent
of Washington physicians agree that children get too many vaccinations too soon, and four percent would recommend an AVS without parental request. While the majority of physicians recommend the routine schedule, nearly two in three would feel comfortable administering an AVS upon request, and in some cases may actually recommend an AVS for their patients.

Parental concern about childhood vaccines has increased in recent years, as have requests for the use of AVS. Some parents have their children begin following an AVS within the first year of life and these children have a difficult time catching up for daycare or school. Parents using an AVS are more likely to change physicians and utilize alternative medicine, suggesting difficulty finding providers who agree with their views on vaccination. Understanding the characteristics of practices providing care to children following an AVS is important given the physician’s role in the vaccination process. This study utilizes immunization registry data to describe health care practices providing care to children following both the RVS and AVS.

METHODS

Study Population

Vaccinations for children born between January 1, 2009 and August 14, 2011 were obtained from the New York State Immunization Information System (NYSIIS). The NYSIIS contains information on doses of vaccines administered to both children and adults residing in New York State (NYS), outside New York City (NYC). Reporting of immunization information to the NYSIIS is mandated by Public Health Law 2168 for all children age 19 and younger. Participation among physicians is high (90%), and more
than 80% of children 6 years and younger have at least two doses recorded in the system.

Each health care practice and patient has a unique identifier; vaccination coverage is tracked at the practice level, not at the individual health care provider level.

This study was approved by the New York State Department of Health Institutional Review Board.

**Definition of Vaccination Schedules**

Children with immunization records in NYSIIS were classified as following the RVS, an AVS, or an unknown schedule based on immunizations recorded between 42 and 270 days of age (2 to 9 months). Children were classified as following the RVS if on two or more unique vaccination dates at least five of the six recommended vaccines were administered (hepatitis B; diphtheria, tetanus and pertussis; polio; pneumococcal disease; *Haemophilus influenzae* Type B; and rotavirus). The AVS classification was assigned if the child received four or fewer vaccines at all unique vaccination dates or had no record of one or more of the recommended vaccinations. All others were classified as unknown.

**Description of Healthcare Practices**

Children were considered to belong to the healthcare practice who reported the majority their vaccinations. Children with vaccines reported by multiple practices were considered to belong to either the practice that reported the most unique vaccination dates, or the practice with the most recent reporting date in the event of a tie.

The total number of children born January 1, 2009 to August 14, 2011 belonging to each practice was determined. Practices reporting fewer than 10 children during the
study period were excluded from analysis. The number of children belonging to each practice following the RVS, AVS, and unknown schedule as well as the number of children who received at least one dose of each of the six recommended vaccines (Hepatitis B; Rotavirus; Polio; Diphtheria, Tetanus and Pertussis; Pneumococcal; and *Haemophilus influenzae* type B) was also calculated. Practices were classified into four groups according to number of children: 10-99, 100-499, 500-999, and 1000 or more. Self-reported facility classifications were private practice, county department of health clinic, federally qualified health center, hospital-based clinic, or other. Practices were also classified as rural, suburban, or urban based on their address using the 2003 USDA-defined Rural-Urban Continuum codes for New York State.  

**Data Analysis**

The proportion of children in each practice following the RVS, AVS, or unknown schedule was calculated, as was the proportion of children who received at least one dose of each recommended vaccine. The medians number of children was calculated for each size, type, and location category of the health care practice. Due to the non-normal distribution of the proportions, the Kruskal-Wallis test was calculated to compare proportion of AVS by size, type, and location using a two sided alpha value of 0.05 (version 9.2, SAS Institute, Inc., Cary, NC).

**RESULTS**

A total of 273 886 children born between January 1, 2009 and August 14, 2011 and residing in NYS, outside NYC had immunizations reported in NYSIIS between 2 and
9 months of age. The majority of children had vaccinations reported by only one practice (92%), the remaining children had vaccinations reported by two to four practices.

Immunizations for at least 10 children were reported by 1230 NYS practices representing 266,020 children. The majority were private practices (86%, n=1058). Larger numbers of practices also reported serving 10-99 children (52%, n=954) and were located in urban counties (49%, n=606). (Table 1)

Practice size correlated with schedule adherence. (Table 1) The median proportion of children following the RVS among the largest facilities was 78% and dropped to 42% in the smallest facilities (p<0.001). Conversely, the median proportion was highest for AVS among the smallest clinics (26%) and lowest for AVS among the largest facilities (6%) (p<0.001) (Table 1).

Urban practices were more likely to report a higher median proportion of children following an AVS compared to rural and suburban practices (20%, p<0.05), whereas suburban practices were more likely to report a higher median proportion of children following the RVS (61%, p<0.05). (Table 1)

Among clinic types, federally qualified health centers reported both the highest proportions of children following the RVS (65%, p<0.05) and lowest proportions of children following an AVS (6%, p<0.05). (Table 1) The highest proportions of children following an AVS were reported by department of health clinics (20%) and private practices (19%) compared to other facilities (p<0.05). Department of health clinics also reported higher median proportions of children with an unknown schedule (38%, p<0.05) (Table 1).
The majority of children received at least one dose of each recommended vaccine. Rotavirus was the vaccine with the lowest proportion of children receiving at least one dose, 89% of all children in the study received rotavirus vaccine. Small facilities also reported a lower median proportion of children receiving rotavirus (82%) (Table 2).

Urban practices reported the lowest median proportion of children receiving all vaccines except rotavirus vaccine. The median proportion of children receiving rotavirus vaccine was lowest in rural practices (81%). Hospital clinics and department of health clinics reported the lowest median proportion of children receiving each individual vaccine, particularly for Rotavirus (40.2% and 71.7% respectively) (Table 2).

DISCUSSION

This study suggests that childhood vaccine schedule adjustments are not uncommon in New York State—nearly one in four children in NYS, outside NYC, are following an AVS and a majority of providers report at least one child following an AVS within their practice. Smaller health care settings tend to see a greater proportion of children following an AVS, a finding that is consistent with two other recent studies. Healthcare provider knowledge of the vaccination schedule, including catch-up regimens, is associated with pediatric practices who see larger numbers of children, possibly due to frequent use and familiarity. It has also been suggested that practices with more children generally utilize vaccine tracking systems which can calculate immunizations due for providers thus easing the burden of vaccinating children. Large practices are also associated with vaccinating during illness visits, either due to the inability to fit a child back in the schedule quickly for a well-child visit or a better
understanding of vaccine contraindications, a course of action known to increase coverage\textsuperscript{294,295}.

This study also indicates that urban practices have a higher median proportion of children following an AVS while rural practices report lower proportions of children following an AVS. The use of AVS by parents has been associated with increased income and education\textsuperscript{215} as well as the use of alternative providers\textsuperscript{280} which may be more prevalent in urban areas.

Federally qualified health centers had the highest proportion of children following an RVS and lowest proportions of children on an AVS, findings consistent with other studies\textsuperscript{280,293,296}. This may be due to the fact that while serving populations with fewer resources, federally qualified health centers provide parents with a medical home. The reverse could be true for county health departments and hospital clinics which may serve populations without a consistent medical home thus leading to increased proportions of both AVS and unknown schedule children.

Previous studies have indicated that private health insurance and use of pediatricians over family practices was associated with higher proportions of children following an AVS\textsuperscript{189,215,249}. This study was unable to distinguish insurance status and pediatric vs. family practice providers; however, pediatric providers and privately insured children may be more likely found in the in the private practice group, a group with a high median proportion of children following an AVS and low median proportion of children following an unknown schedule..
A low proportion of children receiving rotavirus vaccine were reported at small, rural practices, indicating that factors associated with not receiving rotavirus may be different from those associated with the use of AVS. Unlike use of AVS, receiving rotavirus vaccine may be more associated with many factors including safety concerns, the shortened window for administration (2 to 8 months only), cost, and supply issues. Rural providers in smaller practices may also see fewer cases of severe rotavirus infection requiring hospitalization, thus they may be less likely to encourage parents to administer RV. While a study of U.S. physicians found that only 5% believed that rotavirus disease was not severe enough to require vaccination, it has been shown that vaccination with RV has a wide range of effects including decreased episodes of diarrhea in adults highlighting the importance of vaccination for not just individual but community protection. Rotavirus is also one of the most expensive recommended vaccines. An Oregon study indicated that 43% of rural physicians sometimes refer children elsewhere due to cost and supply issues despite the fact that vaccines for children fund covers the cost of vaccine for some children. Finally, the RVS indicates that rotavirus cannot be administered after 8 months of age, thus physicians who see smaller numbers of children may find the shortened administration age range of the vaccine to be a barrier to vaccination.

Most physicians indicate that concern over the safety and efficacy of vaccination does not prevent them from vaccinating children. However, consistently large numbers of physicians are indicating that they are willing to delay the administration of vaccines to children or use other AVS tactics. The results of this
study indicate potential acceptance of AVS among physicians in NYS, consistent with results from other studies.

This study has a number of limitations. First, reporting of vaccinations to NYSIIS may be incomplete. Alternative medicine providers are more likely to accommodate an AVS and are also less likely to report to vaccination registries\textsuperscript{280}. Consequently, while provider participation in the registry is high, it is possible that providers more supportive of AVS may report less, which would result in an underestimate of the overall AVS rate. In addition, this study could not determine whether missing vaccinations were due to supply, choice, provider recommendation or parental request. Finally, the professional training, specialization and recency of formal medical education of the health care providers in the practices examined in this study are not known. Despite these limitations, these findings are supported by the consistency of the data presented here with physician survey data\textsuperscript{189,193,197,199,201,280,293}.

CONCLUSION

This is the first study to quantify the proportion of children following an alternate vaccine schedule by practice size and type. We found that high proportions of AVS use tend to be more commonly reported by smaller, urban practices. The most recent addition to the schedule (rotavirus vaccine) did not follow the same pattern, indicating that factors associated with rotavirus under-vaccination may differ from those for AVS use in general. Physicians must be adequately prepared to discuss vaccine safety and efficacy with parents, and effective, evidence-based materials to aid in this conversation should be developed
Table 1. Median Proportion of Children on each schedule for type of practice, locality of practice, and size of practice New York State (outside New York City) Study Cohort 2009-2011.

<table>
<thead>
<tr>
<th></th>
<th>Number of Practices</th>
<th>Number of Children represented</th>
<th>Recommended Schedule % (Range)</th>
<th>Alternative Vaccination Schedule % (Range)</th>
<th>Unknown Schedule % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Practice</td>
<td>1058</td>
<td>230,258</td>
<td>54.7 (0.93.32)</td>
<td>18.5 (0.100)</td>
<td>15.4 (0.66.6)</td>
</tr>
<tr>
<td>Hospital</td>
<td>28</td>
<td>11,383</td>
<td>47.3 (0.79.5)</td>
<td>12.8 (0.96.0)</td>
<td>20.3 (2.5-63.2)</td>
</tr>
<tr>
<td>Department of Health Clinic</td>
<td>58</td>
<td>6,325</td>
<td>44.2 (0.75.9)</td>
<td>19.5 (0.69.2)</td>
<td>37.5 (9.1-87.5)</td>
</tr>
<tr>
<td>Federally Qualified Health Center</td>
<td>45</td>
<td>13,146</td>
<td>64.6 (0.91.9)</td>
<td>6.1 (0.64.7)</td>
<td>25.0 (7.5-60.0)</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>4,908</td>
<td>58.3 (0.89.8)</td>
<td>10.9 (0.100)</td>
<td>21.2 (0.80.0)</td>
</tr>
<tr>
<td>Rural Practice</td>
<td>233</td>
<td>35,321</td>
<td>54.2 (0.96.0)</td>
<td>15.4 (0.93.6)</td>
<td>18.6 (0.66.6)</td>
</tr>
<tr>
<td>Suburban Practice</td>
<td>391</td>
<td>82,671</td>
<td>60.7 (0.94.3)</td>
<td>16.7 (0.100)</td>
<td>15.6 (0.65.3)</td>
</tr>
<tr>
<td>Urban Practice</td>
<td>606</td>
<td>148,028</td>
<td>50.0 (0.91.0)</td>
<td>20.0 (0.100)</td>
<td>16.7 (0.69.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number</th>
<th>Median Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-99 Children</td>
<td>634</td>
<td>42.0 (0.95.4)</td>
</tr>
<tr>
<td>100-499 Children</td>
<td>440</td>
<td>60.2 (0.91.9)</td>
</tr>
<tr>
<td>500-999 Children</td>
<td>115</td>
<td>69.5 (0.92.6)</td>
</tr>
<tr>
<td>1000+ Children</td>
<td>41</td>
<td>77.9 (2.9-90.8)</td>
</tr>
</tbody>
</table>

a. Kruskal-Wallis tests for type of practice, location of practice, and size of practice were significant for recommended vaccination schedule, alternative vaccination schedule, and unknown vaccination schedule.

b. Range of values from 1% to 99%
Table 2. Median Proportion of Children receiving at least one dose of each recommended vaccine by type of practice, location of practice, and size of practice. New York State (outside New York City) 2009-2011.

<table>
<thead>
<tr>
<th>Practice Type</th>
<th>Diphtheria, Tetanus, and Pertussis % (Range)</th>
<th>Haemophilus influenza Type B % (Range)</th>
<th>Polio % (Range)</th>
<th>Hepatitis B % (Range)</th>
<th>Pneumococcal % (Range)</th>
<th>Rotavirus % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Practice</td>
<td>100 (93.5-100)</td>
<td>100 (87.5-100)</td>
<td>100 (85.7-100)</td>
<td>97.9 (71.2-100)</td>
<td>99.5 (75.0-100)</td>
<td>89.6 (0-100)</td>
</tr>
<tr>
<td>Hospital</td>
<td>100 (18.0-100)</td>
<td>99.6 (0-100)</td>
<td>99.1 (0-100)</td>
<td>98.1 (0-100)</td>
<td>99.5 (0-100)</td>
<td>40.2 (0-96.4)</td>
</tr>
<tr>
<td>Department of Health Clinic</td>
<td>100 (97.5-100)</td>
<td>99.7 (71.4-100)</td>
<td>100 (75.0-100)</td>
<td>96.6 (75.0-100)</td>
<td>96.9 (71.4-100)</td>
<td>71.7 (0-100)</td>
</tr>
<tr>
<td>Federally Qualified Health Center</td>
<td>100 (99.0-100)</td>
<td>99.7 (90.8-100)</td>
<td>100 (92.3-100)</td>
<td>99.5 (92.5-100)</td>
<td>99.3 (94.7-100)</td>
<td>93.5 (11.8-100)</td>
</tr>
<tr>
<td>Other</td>
<td>100 (97.8-100)</td>
<td>100 (0-100)</td>
<td>100 (0-100)</td>
<td>100 (69.2-100)</td>
<td>100 (0-100)</td>
<td>88.7 (0-100)</td>
</tr>
<tr>
<td>Rural Practice</td>
<td>100 (98.0-100)</td>
<td>100 (92.6-100)</td>
<td>100 (90.6-100)</td>
<td>99.3 (71.4-100)</td>
<td>100 (75-100)</td>
<td>80.6 (0-100)</td>
</tr>
<tr>
<td>Suburban Practice</td>
<td>100 (97.8-100)</td>
<td>100 (85.7-100)</td>
<td>100 (85.7-100)</td>
<td>98.3 (72.7-100)</td>
<td>99.5 (66.7-100)</td>
<td>85.7 (0-100)</td>
</tr>
<tr>
<td>Urban Practice</td>
<td>100 (88.3-100)</td>
<td>99.7 (78.3-100)</td>
<td>99.5 (81.3-100)</td>
<td>97.2 (69.2-100)</td>
<td>99.1 (66.7-100)</td>
<td>91.3 (0-100)</td>
</tr>
<tr>
<td>10-99 Children</td>
<td>100 (81.8-100)</td>
<td>100 (65.5-100)</td>
<td>100 (67.2-100)</td>
<td>97.8 (60.0-100)</td>
<td>100 (42.7-100)</td>
<td>82.0 (0-100)</td>
</tr>
<tr>
<td>100-499 Children</td>
<td>100 (93.3-100)</td>
<td>99.4 (92.8-100)</td>
<td>99.2 (88.3-100)</td>
<td>96.8 (79.2-100)</td>
<td>98.9 (81.7-100)</td>
<td>93.1 (5.3-98.6)</td>
</tr>
<tr>
<td>500-999 Children</td>
<td>99.8 (97.6-100)</td>
<td>99.5 (96.0-100)</td>
<td>99.3 (94.2-100)</td>
<td>97.6 (82.7-99.8)</td>
<td>99.2 (92.8-100)</td>
<td>94.7 (54.8-98.2)</td>
</tr>
<tr>
<td>1000+ Children</td>
<td>99.9 (99.1-100)</td>
<td>99.7 (99.0-99.9)</td>
<td>99.4 (95.6-100)</td>
<td>97.7 (89.1-99.6)</td>
<td>99.4 (94.8-99.8)</td>
<td>95.3 (78.4-98.3)</td>
</tr>
<tr>
<td>State Total</td>
<td>100 (94.2-100)</td>
<td>100 (83.9-100)</td>
<td>100 (83.3-100)</td>
<td>98.0 (71.2-100)</td>
<td>99.5 (70.6-100)</td>
<td>88.9 (0-100)</td>
</tr>
</tbody>
</table>

a. Kruskal-Wallis tests for location of practice, and size of practice were significant rotavirus vaccine and significant by type of practice for Haemophilus influenza Type B, Hepatitis B, and Rotavirus vaccine

b. Range of values from 5% to 95%
Chapter 4. Conclusions

While the proportion of children following an AVS is decreasing among birth cohorts between 2009 and 2011, a trend mostly attributed to increases in rotavirus vaccination, the proportion of children vaccinated following an AVS in NYS, outside NYC, remains at 21% in 2011. Even with an increased number of vaccination visits the majority of these children remained under-vaccinated at age 9 months compared to children following the RVS. Children following an AVS delay vaccination, reduce the number of vaccines given at each visit, spread vaccination out over longer intervals, and refuse specific vaccines. Higher median household income and education are associated with communities having an increased rate of children vaccinated following an AVS; consistent with previously reported characteristics of individuals vaccinated following an AVS\textsuperscript{215}. Finally, children following an AVS are disproportionately vaccinated at smaller urban practices in NYS, outside NYC.

The newest vaccine to the schedule, rotavirus, is not often included when assessing AVS\textsuperscript{175,215}. Rotavirus vaccine was included in the studies presented here for two reasons: 1) rotavirus was added to the RVS in 2006\textsuperscript{25,176} and thus was part of the RVS for all children in this analysis, and 2) any deviation from the RVS is part of the broad definition of AVS and thus any intentional decline of rotavirus vaccination, regardless of whether promoted by parent or physician, is an AVS. Rotavirus refusal was a significant contributor to the selective AVS group. The results of these studies indicate that refusal patterns for rotavirus may be inconsistent with the generalized AVS, thus warranting further study of rotavirus vaccination.
This study has several limitations. While NYSIIS contains information on over 3 million persons vaccinated in NYS, outside NYC, it is still a relatively young registry. As with all registries, reporting of vaccinations to NYSIIS may be incomplete. Children could have received vaccinations outside of NYS or providers may not accurately report all vaccinations, thus leading to data entry errors. However, studies have shown that with good provider participation the accuracy of information contained within an IIS can be high. In addition, intent to follow an AVS can only be inferred from our data; parents were not contacted and medical records were not reviewed. Consistent deviation from the RVS on all vaccination visits indicates the use of an AVS regardless of whose intent it was. The second study also assesses risk factors for AVS at the community level which may not describe all individuals following an AVS. Studies of vaccine refusal have shown that similarities in beliefs are associated with high rates of refusal in communities and that vaccine refusers are similar to AVS users thus indicating that use of AVS may be associated with community characteristics. Finally, the third study cannot determine whether missing vaccinations were due to supply, provider recommendation, or parental request, thus the willingness of providers to administer vaccines at the practice level can only be inferred.

These studies propose a novel method for identifying AVS use through documentation in an immunization registry of consistent deviation from the RVS at all vaccination visits through nine months of age. Other studies assessing AVS outside of the first nine months have been restricted to parental report and physician documentation of parental refusal. However, research shows that parents generally do not understand the RVS and cannot accurately recall their child’s vaccination status, thus
parental report may not accurately measure AVS\textsuperscript{186,203,206,288}. Because physicians do not always document parent refusal, utilization of this method will underestimate the use of AVS\textsuperscript{249}. One other study has assessed the use of AVS among a similar population, defining AVS as limiting physical injections at each visit to two or less\textsuperscript{175}. Vaccine hesitancy has been clearly associated with a fear of multiple injections\textsuperscript{194,204,208}. The use of combination vaccines, particularly Pentacel\textsuperscript{®}, and oral vaccines, such as rotavirus, allow a child to be fully vaccinated without deviating from the RVS with two or fewer injections at most visits\textsuperscript{25}. Published AVSs specifically suggest avoiding combination vaccines because of increased amounts of controversial ingredients, particularly the adjuvant aluminum\textsuperscript{230}. By utilizing a method which looks at vaccine components available individually, as in this undertaking, a more accurate assessment of AVS use can be made in the two-to-nine month age group. That said, the method employed here will underestimate the prevalence of AVS for two reasons. First, because some parents will not begin vaccinating before nine months of age, these children will not be in the database. Second, parents who request unusual deviations from the schedule (aside from reducing the number of vaccines given at one time or selectively refusing a vaccine) will not be identified by this pattern-based method. One final methodological consideration is the inclusion of rotavirus vaccine. Refusal of rotavirus vaccine may be based on factors outside of parental choice or physician recommendation due to the strict age range for this vaccine. Removal of rotavirus from this analysis would reduce AVS rates to approximately 17\%.

In conclusion, the use of AVS in NYS, outside NYC, is a noteworthy cause of under-vaccination among infants two to nine months old. The paucity of studies
evaluating the safety and efficacy of deviations to the RVS indicates that true impact of AVS use on vaccination coverage and timeliness is unknown. Given the high prevalence of children age two to nine months vaccinated following an AVS, the development of methods to accurately classify older children is necessary. Accurate identification and further description of children vaccinated following an AVS is needed to develop effective educational strategies which reassure parents and clinicians about vaccination if adequate coverage is to be sustained.
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## Appendix 1. Additional Tables

### Table 1. National Childhood Vaccine Injury Act – Vaccine Injury Table\(^{18;19}\) for selected vaccines\(^a\)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Illness, disability, injury of condition covered</th>
<th>Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines containing tetanus toxoid (e.g., DTaP, DTP, DT, Td, TT)</td>
<td>A. Anaphylaxis or anaphylactic shock&lt;br&gt;B. Brachial neuritis&lt;br&gt;C. Any acute complications or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed</td>
<td>4 hours&lt;br&gt;2 – 28 Days&lt;br&gt;Not applicable</td>
</tr>
<tr>
<td>Vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis bacteria, or specific pertussis antigen(s) (e.g., DTP, DTaP, P, DTP-Hib)</td>
<td>A. Anaphylaxis or anaphylactic shock&lt;br&gt;B. Encephalopath (or encephalitis)&lt;br&gt;C. Any acute complications or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed</td>
<td>4 hours&lt;br&gt;72 hours&lt;br&gt;Not applicable</td>
</tr>
<tr>
<td>Vaccines containing polio inactivated (e.g., IPV)</td>
<td>A. Anaphylaxis or anaphylactic shock&lt;br&gt;B. Any acute complications or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed</td>
<td>4 hours&lt;br&gt;Not applicable</td>
</tr>
<tr>
<td>Hepatitis B. Vaccines</td>
<td>A. Anaphylaxis or anaphylactic shock&lt;br&gt;B. Any acute complications or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed</td>
<td>4 hours&lt;br&gt;Not applicable</td>
</tr>
<tr>
<td>Haemophilus influenzae type b polysaccharide conjugate vaccines</td>
<td>No Condition Specified</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Rotavirus vaccine</td>
<td>No Condition Specified</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccines</td>
<td>No Condition Specified</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

\(^a\) Effective date July 2011.
Table 2. Claims Filed\(^a\) and Compensated by Vaccine for Selected Vaccines\(^b,19\)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Claims Filed(^b)</th>
<th>Compensated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT (diphtheria-tetanus)</td>
<td>74</td>
<td>23</td>
</tr>
<tr>
<td>DTaP (diphtheria-tetanus-acellular pertussis)</td>
<td>413</td>
<td>154</td>
</tr>
<tr>
<td>DTaP-HepB-IPV (Pediarix)</td>
<td>76</td>
<td>23</td>
</tr>
<tr>
<td>DTaP-Hib (Comvax)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>DTaP-IPV-Hib (Pentacel)</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>631</td>
<td>219</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Inactivated Polio</td>
<td>276</td>
<td>7</td>
</tr>
<tr>
<td>Pneumococcal Conjugate</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>53</td>
<td>15</td>
</tr>
</tbody>
</table>

a. The number of claims filed by vaccine as reported by petitioners in claims since the VICP began on October 1, 1988, which have been compensated or dismissed by the U.S. Court of Federal Claims (Court). Claims can be compensated by a settlement between parties or a decision by the Court.

b. Includes both injury and death.
Table 3. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages — National Immunization Survey, United States, 2011<sup>a</sup> selected vaccines<sup>176</sup>

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>% Coverage</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 doses</td>
<td>95.5</td>
<td>(+0.5)</td>
</tr>
<tr>
<td>≥ 4 doses</td>
<td>84.6</td>
<td>(+1.0)</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>93.9</td>
<td>(+0.6)</td>
</tr>
<tr>
<td>Hib&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 doses</td>
<td>94.0</td>
<td>(+0.6)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Primary series</td>
<td>94.2</td>
<td>(+0.6)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Full series</td>
<td>80.4</td>
<td>(+1.1)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>HepB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 doses</td>
<td>91.1</td>
<td>(+0.7)</td>
</tr>
<tr>
<td>1 dose by 3 days (birth)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>68.6</td>
<td>(+1.3)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 doses</td>
<td>93.6</td>
<td>(+0.6)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥ 4 doses</td>
<td>84.4</td>
<td>(+1.0)</td>
</tr>
<tr>
<td>Rotavirus&lt;sup&gt;e&lt;/sup&gt;</td>
<td>67.3</td>
<td>(+1.3)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4:3:1:3:3:1:4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>68.5</td>
<td>(+1.3)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = confidence interval; DTaP = diphtheria, tetanus toxoids and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria, tetanus toxoids, and pertussis vaccine [DTP] and diphtheria and tetanus toxoids vaccine [DT]); Hib = *Haemophilus influenzae* type b vaccine; HepB = hepatitis B vaccine; PCV = pneumococcal conjugate vaccine.

<sup>a</sup> For 2011 estimates children were born during January 2008 through May 2010.
<sup>b</sup> Primary series: receipt of ≥2 or ≥3 doses, depending on product type received. Full series: receipt of ≥3 or ≥4 doses, depending on product type received (primary series and booster dose).
<sup>c</sup> Statistically significant increase in coverage compared with 2010 (p<0.05).
<sup>d</sup> HepB administered between birth and age 3 days.
<sup>e</sup> Rotavirus vaccine includes ≥2 or ≥3 doses, depending on the product type received (≥2 doses for Rotarix [RV1] and ≥3 doses for RotaTeq [RV5]).
<sup>f</sup> 4:3:1:3:3:1:4 series, referred to as routine, includes ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, full series of Hib (3 or 4 doses, depending on product type), ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV.
Table 4. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages by race/ethnicity$^a$ and poverty level$^b$ — National Immunization Survey, United States, 2011$^c$

| Vaccine | Race/Ethnicity$^a$ |               |               | American Indian/Alaska Native |               |               |                | Poverty level |
|---------|-------------------|---------------|---------------|------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|         | White             | Black         | Hispanic      | Asian                        | Multiracial   | Below         | At or above   |               |               |               |
|         | % (95% CI)       | % (95% CI)    | % (95% CI)    | % (95% CI)                  | % (95% CI)    | % (95% CI)    | % (95% CI)    | % (95% CI)    | % (95% CI)    | % (95% CI)    |
| DTaP    |                   |               |               |                             |               |               |               |               |               |               |
| ≥ 3 doses | 95.5 (±0.7)    | 94.7 (±1.5)   | 95.6 (±1.0)   | 89.6 (±7.3)                 | 97.9 (±1.3)$^f$ | 95.3 (±2.7)   | 94.7 (±1.0)$^f$ | 96.2 (±0.6)   |               |               |
| ≥ 4 doses | 85.0 (±1.3)    | 81.3 (±2.9)$^e$ | 84.1 (±2.2)   | 72.7 (±9.5)$^e$             | 92.0 (±2.5)$^e$ | 87.1 (±3.7)   | 81.0 (±1.9)$^f$ | 86.8 (±1.1)   |               |               |
| Poliovirus | 93.9 (±0.8)    | 93.9 (±1.6)   | 93.8 (±1.4)   | 88.1 (±7.4)                 | 96.5 (±1.7)$^e$ | 93.5 (±3.0)   | 93.6 (±1.0)   | 94.2 (±0.7)   |               |               |
| Hib$^b$ |                   |               |               |                             |               |               |               |               |               |               |
| Primary series | 94.2 (±0.8)    | 93.0 (±1.8)   | 94.5 (±1.2)   | 91.7 (±6.6)                 | 94.6 (±2.3)   | 94.4 (±2.8)   | 92.9 (±1.1)$^f$ | 95.4 (±0.6)   |               |               |
| Full series | 81.0 (±1.4)    | 74.6 (±3.3)$^e$ | 81.6 (±2.2)   | 73.7 (±9.6)                 | 83.5 (±4.7)   | 82.0 (±4.6)   | 75.5 (±2.1)$^f$ | 83.4 (±1.2)   |               |               |
| HepB    |                   |               |               |                             |               |               |               |               |               |               |
| ≥ 3 doses | 90.3 (±1.0)    | 92.1 (±1.8)   | 91.5 (±1.6)   | 92.6 (±6.5)                 | 95.5 (±2.0)$e$ | 90.7 (±3.7)   | 91.8 (±1.2)   | 91.2 (±0.8)   |               |               |
| 1 dose by 3 days (birth)$^b$ | 66.0 (±1.6)    | 73.4 (±3.4)$^e$ | 70.8 (±2.9)$^e$ | 83.6 (±5.9)$^e$            | 69.0 (±6.5)   | 65.2 (±6.0)   | 73.3 (±2.2)$^f$ | 65.6 (±1.6)   |               |               |
| PCV     |                   |               |               |                             |               |               |               |               |               |               |
| ≥ 3 doses | 93.4 (±0.8)    | 93.4 (±1.7)   | 94.3 (±1.2)   | 85.5 (±8.7)                 | 92.5 (±2.9)   | 94.4 (±2.8)   | 93.4 (±1.1)   | 94.0 (±0.7)   |               |               |
| ≥ 4 doses | 85.3 (±1.2)    | 81.3 (±2.8)$^e$ | 84.6 (±2.1)   | 75.3 (±9.3)$^e$             | 84.9 (±4.7)   | 84.0 (±4.2)   | 80.6 (±1.9)$^f$ | 86.9 (±1.1)   |               |               |
| Rotavirus$^c$ | 68.3 (±1.6)    | 62.5 (±3.5)$^e$ | 68.3 (±2.9)   | 57.7 (±9.5)                 | 66.9 (±6.1)   | 67.8 (±5.7)   | 61.1 (±2.4)$^f$ | 71.1 (±1.4)   |               |               |
| Combined series | 68.8 (±1.6)    | 63.7 (±3.7)$^e$ | 69.5 (±2.8)   | 65.9 (±9.5)                 | 70.8 (±6.1)   | 70.9 (±5.5)   | 63.6 (±2.4)$^f$ | 71.6 (±1.5)   |               |
### TABLE 4 continued. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages by race/ethnicity and poverty level — National Immunization Survey, United States, 2011

**Abbreviations:** CI = confidence interval; DTaP = diphtheria, tetanus toxoids and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria, tetanus toxoids, and pertussis vaccine [DTP] and diphtheria and tetanus toxoids vaccine [DT]); Hib = *Haemophilus influenzae* type b vaccine; HepB = hepatitis B vaccine; PCV = pneumococcal conjugate vaccine; a. Child's race/ethnicity was reported by their parent or guardian. Children identified as white, black, Asian, or American Indian/Alaska Native are non-Hispanic. Children identified as multiracial had more than one race category selected. Persons identified as Hispanic might be of any race. b. Poverty level was determined for all children. Children were classified as below poverty if their total family income was less than the poverty threshold specified for the applicable family size and number of children aged <18 years. All others were classified as at or above poverty. Poverty thresholds reflect yearly changes in the Consumer Price Index. Thresholds and guidelines available at [http://www.census.gov/hhes/www/poverty.html](http://www.census.gov/hhes/www/poverty.html). c. Children in the 2011 National Immunization Survey were born during January 2008–May 2010. d. Native Hawaiian or other Pacific Islanders were not included in the table because of small sample sizes. e. Statistically significant difference (p<0.05) in estimate compared with white, non-Hispanic children. f. Statistically significant difference (p<0.05) in estimate compared with children living at or above the poverty level. g. Primary series: receipt of ≥2 or ≥3 doses, depending on product type received; full series: primary series and booster dose includes receipt of ≥3 or ≥4 doses depending on product type received. h. HepB administered between birth and age 3 days. i. Includes ≥2 or ≥3 doses, depending on product type received (≥2 doses for Rotarix [RV1], ≥3 doses for RotaTeq [RV5]). j. 4:3:1:3*:3:1:4 series includes ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, full series of Hib (3 or 4 doses, depending on type), ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV.
Table 5. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages — National Immunization Survey, New York State, excluding New York City, 2011a selected vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>% Coverage</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP ≥ 4 doses</td>
<td>82.0</td>
<td>(±5.5)</td>
</tr>
<tr>
<td>Rotaviruse</td>
<td>60.9</td>
<td>(±7.2)</td>
</tr>
<tr>
<td>4:3:1::3:1:4f</td>
<td>63.7</td>
<td>(±7.5)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = confidence interval; DTaP = diphtheria, tetanus toxoids and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria, tetanus toxoids, and pertussis vaccine [DTP] and diphtheria and tetanus toxoids vaccine [DT]); Hib = *Haemophilus influenzae* type b vaccine; HepB = hepatitis B vaccine; PCV = pneumococcal conjugate vaccine.

a. For 2011 estimates children were born during January 2008 through May 2010
b. Primary series: receipt of ≥2 or ≥3 doses, depending on product type received. Full series: receipt of ≥3 or ≥4 doses, depending on product type received (primary series and booster dose).
c. Statistically significant increase in coverage compared with 2010 (p<0.05).
d. HepB administered between birth and age 3 days.
e. Rotavirus vaccine includes ≥2 or ≥3 doses, depending on the product type received (≥2 doses for Rotarix [RV1] and ≥3 doses for RotaTeq [RV5]).
f. 4:3:1:3:1:4 series, referred to as routine, includes ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, excluding Hib, ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV.
Appendix 2. Organization Chart of Federal Vaccines

Vaccine-related advisory committees. Image: Figure 2 of the Shen AK, Spinner JR, Salmon DA, Gellin, BG. Strengthening the US vaccine and immunization enterprise: The role of the National Vaccine Advisory Committee. Pub Health Rep 2011;126:4-8.
Appendix 3 – Recommended immunization schedule for persons aged 0 through 6 years – United States 2012

**FIGURE 1: Recommended immunization schedule for persons aged 0 through 6 years** — United States, 2012 (for those who fail behind or start late, see the catch-up schedule [Figure 3])

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age</th>
<th>Birth</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
<th>60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (Hep B) vaccine</td>
<td>Minimum age: 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis</td>
<td>DTaP</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib) vaccine</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccine (PCV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella vaccine (Var)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Meningococcal C vaccine</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**RECOMMENDATIONS:**

1. **Hepatitis B (Hep B) Vaccine.** (Minimum age: birth)
   - Birth: Administer monovalent Hep B vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HIB) within 12 hours of birth. These infants should be tested for HBSAg and antibody to anti-HBs (anti-HBs) 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
   - If mother’s HBsAg status is unknown: within 12 hours of birth, administer HepB vaccine for infants weighing ≥2,000 grams, and HepB vaccine plus HIBG for infants weighing <2,000 grams. Determine status: HBsAg status is not possible and, if HBsAg- positive, administer HIBG for infants weighing ≥2,000 grams (no later than age 1 week).
   - Doses after the birth dose:
     - The second dose should be administered at age 1 to 2 months. Monovalent HepB vaccine should be used for doses administered before age 9 weeks.
     - Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine starting as soon as feasible (Figure 3).
   - The minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 6 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose.

2. **Rotavirus (RV) vaccines.** (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-2 [RotaTeq])
   - The maximum age for the first dose in the series is 14 weeks; 0 days, and 6 months, 0 days, for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - Infants who have received 4 doses of a HepB-containing vaccine should be administered 2 doses at age 2 months and 6 months, a dose at 6 months is not indicated.

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.** (Minimum age: 6 weeks)
   - The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the fifth dose.

4. **Haemophilus influenzae type b (Hib) conjugate vaccine.** (Minimum age: 6 weeks)
   - If PRP-OMP (Prevenar/HibTec or HibTec-Hib) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.

5. **Pneumococcal vaccine.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine (PCV7) 2 years for pneumococcal polysaccharide vaccine [PPSV])
   - Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not complies vaccinated for their age.
   - For children who have received 4 doses of a pneumococcal conjugate vaccine (PCV13) at ages 2, 4, 6 months (PCV13), is recommended for:
     - All children aged 24 through 59 months.
     - Children aged 24 through 59 months with underlying medical conditions.
   - Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See MMWR 2010;59(RR-11), available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5911a1.htm.

6. **Inactivated poliovirus vaccine (IPV).** (Minimum age: 8 weeks)
   - If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

---

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip/index.htm), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org). Department of Health and Human Services – Center for Disease Control and Prevention.
Appendix 4.  Evolution of Immunization Programs

Evolution of Immunization Programs. Image: Figure 1. of the Chen RT, Orenstein WA. Epidemiologic methods in immunization programs. *Epidemiol Rev* 1996;18:99-117.
Appendix 5. Dr. Sear’s Alternative Vaccination Schedules

Dr. Bob’s Alternative and Selective Vaccine Schedule through 9 months of age

<table>
<thead>
<tr>
<th>Age of Child</th>
<th>Alternative Schedule Vaccines</th>
<th>Selective Schedule Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth*</td>
<td>HepB</td>
<td>HepB</td>
</tr>
<tr>
<td>2 months</td>
<td>DTaP, Rotavirus</td>
<td>DTaP, Rotavirus</td>
</tr>
<tr>
<td>3 months(^a)</td>
<td>PCV, Hib</td>
<td>PCV, Hib</td>
</tr>
<tr>
<td>4 months</td>
<td>DTaP, Rotavirus</td>
<td>DTaP, Rotavirus</td>
</tr>
<tr>
<td>5 months(^a)</td>
<td>PCV, Hib</td>
<td>PCV, Hib</td>
</tr>
<tr>
<td>6 months</td>
<td>DTaP, Rotavirus</td>
<td>DTaP, Rotavirus</td>
</tr>
<tr>
<td>7 months(^a)</td>
<td>PCV, Hib</td>
<td>PCV, Hib</td>
</tr>
<tr>
<td>9 months</td>
<td>Polio, Flu(^b)</td>
<td>No recommended vaccines</td>
</tr>
</tbody>
</table>

**Abbreviations**

DTaP = diphtheria, tetanus toxoids and acellular pertussis vaccine; Hib = *Haemophilus influenzae* type b vaccine; HepB = hepatitis B vaccine; PCV = pneumococcal conjugate vaccine.

a. Vaccines should be given at shot only visits, a full checkup is not necessary at this time

b. The flu vaccine starts between 6 and 12 months when near flu season

*The birth dose of HepB is only for children who have a close family member who is HepB positive*
Appendix 6. Dr. Cave’s Alternative Vaccine Schedule

Dr. Cave’s Alternative Vaccine Schedule through 9 months of age

<table>
<thead>
<tr>
<th>Age of Child</th>
<th>Alternative Schedule Vaccines&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>Hib</td>
</tr>
<tr>
<td>3 months</td>
<td>PCV</td>
</tr>
<tr>
<td>4 months</td>
<td>Hib &amp;IPV</td>
</tr>
<tr>
<td>5 months</td>
<td>DTaP</td>
</tr>
<tr>
<td>6 months</td>
<td>IPV, PCV</td>
</tr>
<tr>
<td>6 months, 2 weeks later</td>
<td>Hib</td>
</tr>
<tr>
<td>7 months</td>
<td>DTaP</td>
</tr>
<tr>
<td>8 months</td>
<td>PCV</td>
</tr>
<tr>
<td>9 months</td>
<td>DTaP</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- DTaP = diphtheria, tetanus toxoids and acellular pertussis vaccine
- Hib = *Haemophilus influenzae* type b vaccine
- HepB = hepatitis B vaccine
- IPV = inactivated poliovirus vaccine
- PCV = pneumococcal conjugate vaccine
- NO HepB, Proquad, or Comvax
Appendix 7.  Dr. Miller’s Selective Vaccine Schedule

Dr. Miller’s Selective Vaccine Schedule through 9 months of age

<table>
<thead>
<tr>
<th>Age of Child</th>
<th>Selective Schedule Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td></td>
</tr>
<tr>
<td>5 months</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>7 months</td>
<td></td>
</tr>
<tr>
<td>8 months</td>
<td></td>
</tr>
<tr>
<td>9 months</td>
<td></td>
</tr>
</tbody>
</table>

Dr. Miller believes that no vaccines should be given before 2 years of age then Pertussis, Diphtheria, Tetanus, and the Salk Polio vaccine can be given one at a time with 6 months between each vaccination.
Appendix 8. Variables included in NYSIIS

We are requesting a SAS dataset that contains each of the following data elements for each immunization administered, for all immunizations recorded in the NYSIIS database, for all individuals aged less than 19 who reside in New York State outside of New York City.

Client level information
Unique patient-level client ID number
Birth date
State of residence
County of residence
Zip code of residence
Gender
Race
Ethnicity

Vaccine level information
Vaccine
Multiple Antigen Indicator
Individual Antigen Indicator
Vaccination date
Data entry source
Trade name
Historical Indicator
Ordinal position in series
Number of vaccines in series
Validity of dose based on ACIP schedule
Funding Type
Insurer

Provider level information
Provider organization ID number
State
County
Organization type
Organization name
Organization Zip Code
Appendix 9. New York State Department of Health IRB approval

July 25, 2012

Jessica Nadeau, MPH
NYS Dept. of Health
ESP Corning Twr, Rm. 651
Albany NY 12237

RE: Approval of Protocol Change Application
12-0228: Evaluation of Vaccine Utilization Patterns Among Children and Young Adults in NYS Using the NYS Immunization Information System (NYSIS)

Dear Ms. Nadeau:

The New York State Department of Health Institutional Review Board has reviewed your application for revision of the study listed above. The proposed revisions will change the study designation from exempt to expedited category 5 - research involving materials that have been collected, or will be collected solely for non-research purposes. The requested revision involves additional variables added to the dataset. The change minimally affects the risk/benefit ratio, but does not substantially change the specific aim/design of the study.

This is to confirm that your request for revision has been approved. You are granted permission to conduct your study as revised effective immediately. The date for continuing review remains unchanged at April 29, 2013, unless closed before that date.

Please note that any further changes to the study must be promptly reported to the IRB. Feel free to contact the IRB office at (518) 474-8539 or via fax (518) 408-1423 if you have any questions regarding this approval or require further information.

Sincerely,

Carolyn Y. Reed, C.I.M.
IRB Administrator I

#3405
Appendix 10. SUNY Albany Approval Letter

<table>
<thead>
<tr>
<th>Approved under Exempt Category:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1 – Research conducted in established or commonly accepted educational settings involving normal educational practices.</td>
</tr>
<tr>
<td>☑ 2 – Research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior.</td>
</tr>
<tr>
<td>☐ 3 – Research involving the use of educational tests, interview procedures not exempt under Category 2 if subjects are appointed public officials or research conducted under federal statute requiring confidentiality be maintained throughout the research and thereafter.</td>
</tr>
<tr>
<td>☑ 4 – Research involving collection or study of existing date, documents, records, pathological specimens or diagnostic specimens.</td>
</tr>
<tr>
<td>☑ 5 – Research and demonstration projects conducted by or subject to approval of federal Department or Agency heads and designed to study, evaluate, examine public benefit or service programs.</td>
</tr>
<tr>
<td>☑ 6 – Taste and food quality and evaluation/consumer acceptance studies</td>
</tr>
</tbody>
</table>

1. Provisions of Approval: the determination is valid until the expiration date above. If your research is expected to continue beyond this expiration date, you must submit a new protocol. You are required to maintain IRB approval for as long as the study remains active.

2. All recruitment materials and methods must be approved by the IRB (as part of the determination of exempt from IRB review) prior to being used.

3. Informed Consent: An adequate standard of informed consent has been met when required.

4. Principal Investigator Responsibilities: It is the responsibility of the PI to ensure that all investigators and staff associated with this study meet the training requirements for conducting research involving human subjects, promptly report any changes in research activity to ORRC, keep appropriate research records, and comply with all University at Albany Policies, federal, state and local laws, Declaration of Helsinki and the Belmont Report.

5. Research Records: Accurate and detailed research records must be maintained. All research records (including all IRB correspondence) must be kept for a minimum of 3 years after the completion of the research. This research is subject to an audit under the terms of the IRB’s Quality Improvement Program.

6. Modifications: All protocol modifications must be IRB approved prior to implementation. Modifications include (but are not limited to) study personnel, research instruments, protocol procedures, and/or addition of funding source.

7. Funded Research: If your research is funded or otherwise sponsored research, you must submit any changes to the grant to ORRC with the human subjects section(s) highlighted. This is true whether the source of funding is internal or external.

8. Study Closure: A study is considered to be open and active until the protocol has reached its Expiration Date or the investigator has submitted a Closure Form (available at www.albany.edu/researchcompliance/Forms.html). Until a Closure Form is received, IRB oversight of the research will remain active. A closure notice/reminder will be sent to you, but it is your responsibility to ensure that you submit an updated protocol and receive an approval in a timely manner.

9. Unanticipated or adverse events: All unanticipated or adverse events must be reported to the IRB within 5 days.

10. Other:

cc: McNutt, Louise-Anne

Office of Regulatory Research Compliance, LCSB 28
1400 Washington Ave, Albany, NY 12222
m: 518-442-9050  r: 518-442-9997
www.albany.edu/orrc  e-mail: IRB@albany.edu

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