The Childhood Vaccine Series: Balancing Health, Safety and Stakeholder Concerns

Following today’s recommended childhood immunization schedule results in improved protection against at least 14 different diseases during the first years of life. As the series continues to evolve, parents and scientists alike are working to ensure the childhood series is safe, while looking for ways to make compliance even easier.

By Hillary Johnson, MHS
In January 1925, a relay of 20 mushers and 150 sled dogs raced 674 miles across the U.S. territory of Alaska. The trip along the Nenana-to-Nome Trail usually took 15 to 20 days, but on this occasion, the mushers were not afforded such luxury. Days earlier, Nome doctor Curtis Welch had frantically sent out telegrams requesting antitoxin to help curb an outbreak that had already killed two children and had the potential to nearly wipe out the remote town of 10,000 people. The culprit, diphtheria, was a highly infectious respiratory tract illness known at the time as “the strangling angel of children.” Complications from toxin-producing bacteria C. diphtheriae included the growth of a leathery membrane in the pharynx, which could lead to airway obstruction, coma and death.

Government officials had located the closest supply of antitoxin — hundreds of miles away in the city of Anchorage. Because Nome had no viable roads, air service or winter-accessible ports, Alaska’s Territorial Governor Scott Bone determined a dog sled relay was the best option for delivering the lifesaving drugs. Through radio and newspapers, the nation anxiously followed what became known as the Great Race of Mercy. On Feb. 2, 1925, the anchoring dog sled arrived with the antitoxin in a record-breaking five days and seven hours. Although at least five children died during the outbreak, countless additional lives were ultimately saved through antitoxin administration and quarantine. (The Great Race of Mercy would also serve as a cornerstone event for what would later become the Iditarod Trail Race we know today.)

With only one case reported in 2012, and less than 60 national cases of diphtheria total since 1980, a U.S. parent’s most significant encounter with diphtheria today is likely through the fact sheet they receive at their child’s immunization appointments. However, diphtheria was once a significant cause of illness and death in the U.S., with an average of 100,000 to 200,000 cases and 13,000 to 15,000 deaths per year reported in the 1920s. Diphtheria antitoxin, first used in the U.S. in the 1890s, provided some treatment relief, but it was only helpful in neutralizing early circulating (unbound) toxins, and it was unable to assist when toxins had already fixed to the body’s tissues. (Thus, the incredible importance of timely administration.) Prevention through diphtheria vaccine would not be possible until its development in the 1920s and widespread use in the 1930s.

Thanks to achievements in vaccine research, manufacturing and production technologies over the last century, diphtheria and many more infectious diseases are dwindling worldwide. Throughout these decades, a recommended childhood schedule for vaccination was published periodically in response to new vaccine developments and changes in epidemiology. Since 1995, however, the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) have initiated a review and official publication of an updated schedule annually.

Addressing Parent Concerns

The U.S. childhood immunization schedule has changed significantly over the years, incorporating new vaccines as appropriate, and discontinuing outdated vaccines as technology and disease patterns evolve. The list of recommended vaccinations can appear overwhelming to the new parent, and on the surface (when compared to the list of recommendations from previous decades) has led many to wonder if today’s child is receiving “too many vaccinations too soon.”

In March, the Journal of Pediatrics published a study examining that exact question. The study not only scrutinized how many overall vaccines a child was given and the maximum number of vaccines in one day, but specifically looked at the number of antigens within each vaccine that a child would be exposed to during the first two years of life. (Antigens are the immune-stimulating substances within a vaccine that prompt a body's immune system to recognize and destroy pathogens.)
that contain them.) Dr. Frank DeStefano, the lead researcher and director of the Immunization Safety Office at the Centers for Disease Control and Prevention (CDC), points out that antigenic composition of some vaccines has changed over time, and a complete assessment of the antigenic content of vaccines should take into account all of the antibody-stimulating proteins and polysaccharides in each vaccine, not just the total number of shots.8

For example, previous whole-cell pertussis vaccines contained upwards of 3,000 bacterial proteins. But with advancements in protein purification and the specific identification of proteins responsible for evoking protective immune responses, scientists were able to develop the current purer, acellular vaccine of today, in which only four proteins are needed.9 "Although the current vaccine schedule contains more vaccines than the schedule in the 1990s," said Dr. DeStefano, "the maximum number of antigens a child could be exposed to by 2 years of age in 2013 is 315, compared with several thousand in the late 1990s."10

In Dr. DeStefano’s study, he compared 752 children without autism to 256 children with autism spectrum disorder (ASD) and examined their antigen exposure. The study concluded that for both groups, the antigen exposure was the same, however measured (in one day or over the first two years).11 “There was no association between antigenic exposure and the development of autism,” Dr. DeStefano told CNN.11

Addressing these parental concerns is crucial, as a recent survey found that more than 10 percent of parents are refusing or delaying vaccination, with most believing that a delay in vaccinations is safer than providing them in accordance with CDC’s recommended vaccination schedule.12

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Fewer Needles Through the Promotion of Combination Vaccines

Despite the fact that children today may actually be exposed to fewer antigenic proteins and polysaccharides in today’s vaccines than 20 years ago, a needle stick is still a needle stick. Any parent who has accompanied their little one into the pediatrician’s office for an immunization visit knows the torture associated with seeing them so uncomfortable. Luckily, combination vaccines are leading the way in reducing the number of needle sticks a child receives, and they have other indirect benefits as well.

Combination vaccines work by merging into a single product antigens that prevent different diseases. The first such combination was developed in 1948, when scientists merged diphtheria, tetanus and pertussis vaccines into one vaccine, called DTP.10 Later, in 1971, scientists merged measles, mumps and rubella vaccines into one product, called MMR. There have since been new reformulations of these and other combination vaccines, all with the goal of improving the vaccine and reducing the number of injections a child receives. (In fact, today only various combination vaccines are available in the U.S. for these six diseases.)

However, reducing needle sticks is not the only rationale behind combination products. Combination vaccines may help in timely vaccination coverage by ensuring a child receives all the recommended vaccines at a particular visit (especially if there is a risk a parent may prefer a minimum number of injections, provoking them to spread out vaccinations across multiple visits). Combination vaccines also reduce the cost of stocking multiple individual products and can reduce multiple administration fees. Admittedly, the price of a new combination vaccine may not always be less than the summed cost of similar individual component vaccines, yet when taking into account both direct and indirect costs, combination products may still represent a better economic value.13 With studies showing comparable efficacy across numerous single and combination vaccines,14 they are a no-brainer for many parents. This appeal to parents and pediatricians alike means the occasional manufacturing delay can lead to national shortages (such as the one experienced by Sanofi Pasteur’s Pentacel vaccine [a combination vaccine containing diphtheria, tetanus, pertussis, polio and Hib] in 2012 and into 2013).

Since 1999, the ACIP has generally recommended the use of licensed combination vaccines over separate injections of their equivalent component vaccines whenever possible15 (an exception being the first dose of MMRV [measles, mumps, rubella and varicella], discussed below). Licensed combination vaccines can be used whenever a patient is due for one or more of the components within the combination, provided the
other combination components are not contraindicated for that dose in the series. For example, some combination vaccines such as Peditarix (DTaP-IPV-HepB) mean a child may receive an extra dose of hepatitis B vaccine in their childhood series, but CDC has not found this to be harmful.

Peditarix and Pentacel, addressing a maximum of five diseases each, remain the most comprehensive combination vaccines approved within the U.S. at this time, although some areas of the world are examining hexavalent options as well. (In developing countries, where disease rates are often greater, cold storage may be limited and children have fewer opportunities for vaccination, combination vaccines are more than a convenience, they are a necessity.)

**MMRV Returns as an Option**

It was not too long ago that varicella (more commonly known as chicken pox) was a standard childhood disease. So recently, in fact, that some parents today first learn there is a chicken pox vaccine at their child’s 12-month immunization appointment. Occasionally, a parent may even wonder if the vaccine is necessary. After all, they survived childhood chicken pox, didn’t they? (CDC generally considers most people born in the U.S. before 1980 likely to have had varicella at some point.)

Prior to the varicella vaccine, approximately four million cases of varicella occurred annually. What many parents don’t realize, however, is that before the vaccine, 150,000 to 200,000 of those varicella cases developed complications, 10,000 required hospitalization and 100 people would die each year. (Not to mention that varicella infection leaves you vulnerable to shingles, an incredibly painful skin rash, later in life.) The varicella vaccine first became licensed in 1995 as a single antigen vaccine, and then joined with the MMR vaccine to form the combination MMRV vaccine in 2005.

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Supplies of combination MMRV became temporarily unavailable due to manufacturing constraints (unrelated to efficacy or safety) in 2007 and did not widely return to the market until 2012. In the interim, the ACIP examined post-licensure data and concluded that children aged 12 months to 23 months receiving the combination vaccine had an increased risk for febrile seizures (this was not the case for older children). As a result, the ACIP now recommends use of separate MMR and varicella vaccines for children aged 12 months to 47 months, and use of the combination vaccine MMRV for children aged 4 years to 6 years. This recommendation exemplifies a responsive immunization system that follows the data and responds accordingly as needed.

**Pertussis on the Rise Across the U.S.**

Reports of soaring whooping cough incidence dominated the news in 2012. With more than 41,000 cases of pertussis reported nationally, the U.S. has not seen such record-breaking numbers since the 1950s. Pertussis, commonly known as whooping cough, is an infection in which the bacteria attach to the cilia of the respiratory system. The bacteria produce toxins that paralyze the cilia, preventing the respiratory tract from clearing away pulmonary secretions. Classic symptoms for pertussis include a pronounced “whooping cough” as patients experience difficulty breathing and attempt to expel the thick mucus from their throat and lungs. Pertussis can affect people of any age, but can be particularly severe in infants and young children.

Recent pertussis outbreaks highlight the challenges associated with an immunization program that must balance both risk of disease and concerns about safety. CDC believes waning immunity and recent changes in pertussis vaccine formulation...
are likely contributing to the outbreaks. New data are showing that immunity in children vaccinated with the current acellular pertussis vaccine formulation may wane more rapidly than in children vaccinated with the previous whole-cell pertussis vaccine formulation phased out in the 1990s.23

**Following the recommended childhood vaccination schedule is still one of the most effective ways to protect your child against disease.**

At the time the ACIP recommended the switch, whole-cell pertussis vaccines were associated with higher rates of minor and transient adverse events (or side effects) such as pain, swelling and fever, as well as some rare, but serious neurologic side effects.9 While not all studies were consistent in linking the vaccine to the more severe neurological problems, the U.S. elected to switch to an acellular pertussis vaccine with a better safety profile.24 Now, as the first generation of children solely vaccinated with acellular pertussis vaccine completes their childhood series, scientists are better able to examine potential gaps in immunity coverage.

It is important to note that waning immunity is not only just associated with pertussis vaccination; studies show that even if individuals are directly infected with Bordetella pertussis, they do not develop lifelong immunity and would be susceptible to pertussis again later in life.22 But with the acellular pertussis vaccine, we may have sacrificed stronger immunity for a safer vaccine.9 Researchers are currently examining the impact of the acellular vaccine series, and parents should not be surprised if an enhanced booster dose schedule for adolescents and adults appears in the next few years to combat this waning immunity.

**Strategies to Protect Our Infants**

Although symptoms for pertussis may be milder in adults than in infants and young children, adults are still the most common sources of infection in children; thus, adults and children should both be vaccinated. And when it comes to the smallest of infants, this is particularly important. Of the 18 pertussis-related deaths in 2012, most occurred in infants too young to be vaccinated.26 Previous strategies to protect this vulnerable age group have centered around “cocooning,” or the idea that you create a circle of protection by vaccinating the primary caregivers around an infant. But in light of the national outbreaks and new safety and immunogenicity data, the ACIP published additional guidelines in February recommending that pregnant women receive a Tdap (tetanus, diphtheria and acellular pertussis combination vaccine) with each pregnancy.25

This recommendation is particularly significant, and the ACIP examined many factors when considering this step (previous recommendations have indicated only one lifetime Tdap for all individuals). The idea is to protect infants when they are most vulnerable (in the first few months of life before vaccination). This is achieved indirectly by ensuring the mother is protected, and directly by maximizing transplacental maternal antibodies transferred to the infant. Data now indicate that by vaccinating a mother during pregnancy, we can prevent more hospitalizations and deaths than by vaccinating after pregnancy. They have even found the best stage of pregnancy (between 27 weeks and 36 weeks gestation) to ensure maximum antibody transfer. Because a mother’s antibodies will gradually wane, this new recommendation for each pregnancy ensures that subsequent infants also achieve high levels of protection.

**The Safest Bet Is Timely Vaccination**

Following the recommended childhood vaccination schedule is still one of the most effective ways to protect children against
In January, the Institute of Medicine (IOM) published a report titled *The Childhood Immunization Schedule and Safety, Stakeholder Concerns, Scientific Evidence, and Future Studies*. Through analysis of available research, current monitoring systems and stakeholder input, the IOM found no evidence that the current childhood immunization schedule is unsafe. In fact, “rather than exposing children to harm, following the complete immunization schedule is strongly associated with reducing vaccine-preventable diseases.” As the number of diseases preventable through vaccination continues to expand, innovations such as combination vaccines are making compliance with the childhood vaccine series even easier.

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**References**