Vaccine Spotlight

Quadracel: Vaccination Against Diphtheria, Tetanus, Pertussis, and Poliomyelitis in Children

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ABSTRACT

Introduction: Vaccinations in school-aged children are required by state and local law to maintain high vaccination coverage rates, as well as low rates of vaccine-preventable diseases. Diphtheria, tetanus, and pertussis are childhood diseases that can be life threatening; poliomyelitis, another childhood disease, can be disabling. In turn, vaccinations were developed to provide protection against these diseases. Today, several vaccinations are recommended for children, including but not limited to diphtheria, tetanus, and pertussis (DTaP) and poliomyelitis (IPV). DTaP requires five doses, and IPV requires four. Quadracel (diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine, Sanofi Pasteur Inc.) is a new vaccination developed to condense the last dose of both DTaP and IPV so they do not have to be given separately, thus reducing the total number of vaccinations required.

Discussion: The Quadracel vaccine is an option for use in children who are completing the DTaP and IPV series. In a randomized, controlled, phase 3, pivotal trial, Quadracel proved to be as efficacious and safe as Daptacel (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, Sanofi Pasteur Inc.) and IPOL (poliovirus vaccine inactivated, Sanofi Pasteur Inc.), given separately, to children between the ages of 4 and 6 years.

Conclusion: Quadracel should be recommended to parents who have children between the ages of 4 and 6 years who meet the necessary administration criteria and need to finalize their DTaP and IPV series. Quadracel’s administration in the vaccination series replaces one additional injection, which may benefit children who are afraid of receiving shots and parents who need to schedule one less doctor’s appointment.

Keywords: Quadracel, vaccine, Pentacel, Daptacel, DTaP, IPOL, IPV

INTRODUCTION

Vaccinations in school-aged children are required by state and local law to maintain high vaccination coverage rates, as well as low rates of vaccine-preventable diseases. Vaccinations within the United States have become controversial among parents who do not want to have their children vaccinated due to concerns that vaccinations are harmful to their children’s health and well-being. Many myths have led some parents to believe that vaccines can in turn cause autism because of the chemical thimerosal, a mercury-based preservative, within the vaccines. Although some diseases are not as prevalent as they were 60 years ago, this should not influence the decision to vaccinate children or suggest that vaccines are unnecessary. As a result of the development of vaccines, diseases such as smallpox have been completely eradicated.

Before vaccinations, measles was a common disease in the United States. Once a vaccine was developed, the documented number of measles cases decreased by more than 99%, thus making it a rare disease. However, measles still exists around the world. To this day, the disease is not completely eradicated, even within the United States. For example, in 2015, 189 people from 24 states and the District of Columbia were reported to have measles, and the majority of those people were unvaccinated.

Diphtheria, tetanus, and pertussis are childhood diseases that can be life threatening; poliomyelitis, another childhood disease, can be disabling. Diphtheria, tetanus, and pertussis are caused not only by bacteria, but by the toxins they produce. Because of the severity of these infections and their potential to cause mortality, the diphtheria, tetanus, and pertussis (DTaP) vaccine was created to prevent both children and adults from infection by these diseases. Poliovirus causes poliomyelitis, a disease that attacks the nervous system, causing irreversible paralysis. In turn, the inactivated poliovirus vaccination (IPV) series was developed for prevention of this debilitating disease.

Several vaccinations are needed for children to provide coverage against diseases such as these. More specifically, five doses of vaccine are required for DTaP, and four doses are needed for IPV. Quadracel (diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine, Sanofi Pasteur Inc.) is a new vaccination developed to condense the last dose of both DTaP and IPV so that the two scheduled doses do not have to be given separately, thus reducing the total number of vaccinations required.

INDICATION AND USAGE

Quadracel is a vaccine indicated for the active immunization of diphtheria, tetanus, pertussis, and poliomyelitis. It is approved by the Food and Drug Administration for use in children ages 4 to 6 years as a fifth dose for the DTaP vaccination series and as a fourth or fifth dose in the IPV series in children who have already received four doses of Pentacel (diphtheria and

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tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and haemophilus b conjugate, Sanofi Pasteur Inc.) and/or Daptacel (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, Sanofi Pasteur Inc.). The recommended schedule of vaccination appears in Table 1.

### VACCINE INGREDIENTS

#### Active Ingredients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>2 months 4 months 6 months 15 to 18 months 4 to 6 years</td>
</tr>
<tr>
<td>IPOL</td>
<td>2 months 4 months 6 to 18 months 4 to 6 years</td>
</tr>
</tbody>
</table>

* Quadracel would be considered as the fifth dose of the DTaP vaccination series as well as the fourth dose of the IPOL vaccination series.

#### Inactive Ingredients

- The diphtheria, tetanus, and pertussis antigens are combined with aluminum phosphate, 2-phenoxyethanol, and water for injection.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

**Diphtheria**

This acute disease is caused by toxigenic strains of *Corynebacterium diphtheriae*. Protection against this disease is due to the development of neutralizing antibodies in diphtheria toxin. A serum diphtheria antitoxin level of at least 0.01 IU/mL is generally regarded as protective and has been associated with long-term protection.

**Tetanus**

This acute disease is caused by an extremely potent neurotoxin produced by the organism *Clostridium tetani*; protection against this disease is due to the development of neutralizing antibodies in tetanus toxin. A serum antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered minimal protection level, but 0.01 IU/mL or more of Quadracel, measured by the enzyme-like immunosorbent assay (ELISA) in clinical studies, is considered protective.

**Pertussis**

Known as whooping cough, pertussis is a respiratory disease caused by the organism *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of or immunity to pertussis has not been clearly defined.

### PIVOTAL CLINICAL TRIAL

#### Study Overview

A randomized, multicenter, controlled, phase 3 study was designed to compare the safety and immunogenicity of the Quadracel vaccine with the Daptacel (DTaP) and IPOL (poliovirus vaccine inactivated, Sanofi Pasteur Inc.) vaccines in children 4 through 6 years of age who were previously vaccinated with Daptacel and/or Pentacel. This study enrolled a total of 3,372 participants, who were randomized and vaccinated at 70 clinical sites in the United States and Puerto Rico.

Results were collected by comparing booster response rates of diphtheria, pertussis, and tetanus, as well as geometric mean concentration (GMC) and measured ELISA, following Quadracel administration to subjects vaccinated with Daptacel and IPOL as a fifth dose. Inactivated poliovirus vaccine booster response rates were also compared and measured by neutralizing assay following Quadracel administration to subjects vaccinated with Daptacel and IPOL, as well as the polio (types 1, 2, and 3) geometric mean titer.

A safety assessment was conducted when Quadracel was administered as a fifth dose booster vaccine in participants who were previously vaccinated with Daptacel and Pentacel vaccines.

### Results

Antibody levels of diphtheria, tetanus, pertussis, and poliovirus antigens were measured in sera prior to vaccination and 28 days after vaccination. Results compared the GMC and ELISA of pertussis, diphtheria, and tetanus between Quadracel and Daptacel and IPOL after administration. Quadracel was shown to be noninferior to Daptacel and IPOL vaccines administered concomitantly at separate sites. In addition, a safety assessment was conducted showing that Quadracel had similar safety immunogenicity profiles as compared to separately adminis-

### Table 1 Pediatric Vaccination Schedule

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age at 1st Dose</th>
<th>Age at 2nd Dose</th>
<th>Age at 3rd Dose</th>
<th>Age at 4th Dose</th>
<th>Age at 5th Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>2 months</td>
<td>4 months</td>
<td>6 months</td>
<td>15 to 18 months</td>
<td>4 to 6 years</td>
</tr>
<tr>
<td>IPOL</td>
<td>2 months</td>
<td>4 months</td>
<td>6 to 18 months</td>
<td>4 to 6 years</td>
<td></td>
</tr>
</tbody>
</table>

*DTaP = diphtheria, tetanus, pertussis; IPOL = inactivated poliovirus.*

### Table 2 Booster Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Quadracel (%)</th>
<th>Daptacel + IPOL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-Diphtheria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booster response</td>
<td>97.3</td>
<td>99.2</td>
</tr>
<tr>
<td>Pre-vaccination % ≥ 0.1 IU/mL</td>
<td>90.7</td>
<td>83.1</td>
</tr>
<tr>
<td>Post-vaccination % ≥ 0.1 IU/mL</td>
<td>100.0</td>
<td>99.6</td>
</tr>
<tr>
<td>Post-vaccination % ≥ 1.0 IU/mL</td>
<td>99.6</td>
<td>99.6</td>
</tr>
<tr>
<td>Post-vaccination GMC (IU/mL)</td>
<td>18.6</td>
<td>15.5</td>
</tr>
<tr>
<td><strong>Anti-Tetanus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booster response</td>
<td>84.2</td>
<td>84.3</td>
</tr>
<tr>
<td>Pre-vaccination % ≥ 0.1 IU/mL</td>
<td>91.7</td>
<td>89.1</td>
</tr>
<tr>
<td>Post-vaccination % ≥ 0.1 IU/mL</td>
<td>100.0</td>
<td>99.2</td>
</tr>
<tr>
<td>Post-vaccination % ≥ 1.0 IU/mL</td>
<td>98.9</td>
<td>96.8</td>
</tr>
<tr>
<td>Post-vaccination GMC (IU/mL)</td>
<td>6.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*IPOL = poliovirus vaccine inactivated; GMC = geometric mean concentration.*
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Table 3 Common Side Effects Associated With Quadracel

<table>
<thead>
<tr>
<th>Clinically Significant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
<td>&gt; 75%</td>
</tr>
<tr>
<td>Increased arm circumference</td>
<td>&gt; 65%</td>
</tr>
<tr>
<td>Erythema</td>
<td>&gt; 55%</td>
</tr>
<tr>
<td>Swelling</td>
<td>&gt; 40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common Systemic Reactions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Malaise</td>
<td>&gt; 35%</td>
</tr>
<tr>
<td>Headaches</td>
<td>&gt; 15%</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS

The most common side effects associated with Quadracel are reported in at least 1% of children seven days after receiving this vaccine. These effects and prevalence rates can be found in Table 3.

DRUG INTERACTIONS

The immune response to Quadracel may be reduced when it is taken concomitantly with immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids. Quadracel may be administered with the measles, mumps, and rubella and varicella vaccines as long as they are administered with different syringes and at different injection sites.

CONTRAINDICATIONS

Quadracel is contraindicated in children with hypersensitivity to any of the ingredients in the vaccine. In addition, it is contraindicated in those with encephalopathy (e.g., prolonged seizures, coma, decreased brain function) within seven days of a prior dose of a vaccine containing pertussis and in children with a progressive neurological disorder (e.g., progressive encephalopathy, infantile spasms, uncontrolled epilepsy).

WARNINGS AND PRECAUTIONS

Acute Allergic Reactions

Epinephrine hydrochloride solution and other appropriate agents and equipment must be available for immediate use in case of anaphylactic reaction or acute hypersensitivity.

Adverse Reactions Following Prior Pertussis Vaccination

If any of the following events have occurred within a certain time period after receiving a pertussis vaccination, the decision to administer Quadracel should be based on careful consideration of benefits and risks:

- Temperature of 105°F or higher within 48 hours, with no other identifiable cause
- Collapse or shock-like state within 48 hours
- Persistent, inconsolable crying lasting three hours or more within 48 hours
- Seizure with or without fever within three days

Guillain–Barré Syndrome

Guillain–Barré syndrome is an autoimmune disease in which the body’s immune system attacks its own peripheral nerves and damages the myelin insulation that surrounds the nerves. Symptoms of weakness or a tingling sensation in the legs can be seen with this syndrome. If these symptoms occur within six weeks of administration of a vaccine containing tetanus toxoid, the decision to give Quadracel should be based on careful consideration of the potential benefits and possible risks.

Limitations of Vaccine Effectiveness

Quadracel may not protect all individuals and should not be used in adults.

Altered Immunocompetence

If administered to immunocompromised patients, including those using immunosuppressive agents, the expected immune response may not be obtained; therefore, immune protection may not be provided against the intended diseases.

DOSAGE AND ADMINISTRATION

Quadracel is a suspension for intramuscular injection only, supplied in 0.5-mL single-dose vials. It is administered intramuscularly into the deltid muscle of the upper arm. It should not be administered directly into the veins. The vial must be shaken just before use until a uniform, white, cloudy suspension results. Quadracel should not be reconstituted or mixed with any other vaccine. If there are any signs of tearing or tampering on the packaging, the vaccine should not be used.

STORAGE AND HANDLING

Quadracel should be refrigerated and stored at 35°F to 46°F (2°C to 8°C). It should not be frozen. Any Quadracel product that has been exposed or may have been exposed to freezing should not be used because freezing destroys the vaccine. Always check the expiration date on the label before administering. Expired product should never be used.

COST

The average wholesale price (AWP) for a 0.5-mL dose of Quadracel is $119. In comparison, the combined AWP of the separate DTaP and IPV final vaccinations is $137. Pentacel, a combination vaccine that may be considered instead of Quadracel, is priced at $99 for a single dose.

CONCLUSION

Quadracel should be recommended to parents who have children between the ages of 4 and 6 years who meet the administration criteria and need to finalize their DTaP and IPV series. Quadracel’s administration in the vaccination series replaces one additional injection, which may benefit those children who are afraid of receiving shots. This may also mean having one less doctor’s appointment, which could benefit a parent or legal guardian’s schedule. The cost of Quadracel is comparable to the other vaccines that may be considered for this immunization, so cost should not be an issue. Although the Quadracel vaccine may not protect everyone who has received the vaccination, it has proven to be both immunogenic and safe in clinical trials.

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REFERENCES


