Massachusetts Department of Public Health
Massachusetts Vaccine Purchasing Advisory Council (MVPAC) Meeting

Date: Thursday, October 17, 2013
Time: 4-6 PM
Location: Massachusetts Medical Society, 860 Winter Street, Waltham, MA 02451
Commonwealth Conference Room

MVPAC Council Members

Ronald Adler, MD
Kevin Cranston, MDiv
Marie DeSisto, RN, MSN
Benjamin Kruskal, MD, PhD
Thomas Hines, MD
Susan Lett, MD, MPH
Cody Meissner, MD
David Brumley, MD
Richard Moriarty, MD
David Norton, MD
Sean Palfrey, MD
Ronald Samuels, MD, MPH
Kate Wallis, RN, BSN
Marissa Woltman, MD

Additional Attendees

Beth English, MPH, MDPH
Larry Madoff, MD, MDPH
Bob Morrison, MDPH
Pejman Talebian, MA, MPH, MDPH
Leonard Friedland, GlaxoSmithKline Vaccines
Deborah Gonyar, GlaxoSmithKline Vaccines
Misha Honaker, GlaxoSmithKline Vaccine
Reno Soucy, GlaxoSmithKline Vaccines
Anthony Urciuoli, GlaxoSmithKline Vaccines
Richard Kennan, GlaxoSmithKline Vaccines
Katrina Murphy, Merck Vaccines
Judy Butler, Merck Vaccines
Michael Goldstein, Merck Vaccines
Barbara Homeier, MD, Merck Vaccines
Joe Costello, Novartis Vaccines
Patricia Novy, Novartis Vaccines
Jake Livingstone, Novartis Vaccines
Sherry Schilb, Sanofi Pasteur
Steven Smith, Sanofi Pasteur

<u>Welcome</u>

Mr. Cranston convened the meeting.

Meeting attendees introduced themselves.

<u>DPH Budget and Legislative Updates</u>

Mr. Cranston reminded the group that Cheryl Bartlett is the current Commissioner of Public Health. Ms. Bartlett is a nurse and a long-time community health leader.

Mr. Cranston reported because the Vaccine Trust Fund legislation didn't pass, there still is not adequate funding for MIIS maintenance costs and no ability yet to return to full universal status for pediatric vaccine supply policy. Supplementary budget language has been proposed to help cover the MIIS maintenance costs in this state fiscal year, and it is possible that the full Vaccine Trust Fund legislation could be attached to the supplemental funding bill
Mr. Cranston thanked MCAAP for its continued advocacy on behalf of the bill.

Review of Rotavirus Vaccines

- Overview of products to be considered
- Manufacturer presentations
- Deliberation and voting

Overview of products to be c`onsidered

Dr. Lett directed attendees to the MDPH Rotavirus Vaccine Group handouts.

Dr. Lett reviewed the recommended schedule, available vaccines, cost per dose and whether MDPH provided the Rotavirus vaccines, RotaTeq and Rotarix. She pointed out that she also included information that was requested by providers regarding presentation, reconstitution and application. RotaTeq does not require reconstitution while Rotarix does, the volume per dose is 2 mL for RotaTeq and 1 mL for Rotarix, and there are 3 doses in the series for RotaTeq and 2 doses in the series for Rotarix. The MDPH currently supplies RotaTeq, but with the cost per series being comparable there would not be a significant budget impact if the committee decided to recommend offering Rotarix.

Dr. Lett introduced Dr. Meissner to present data on Rotavirus vaccines and intussusception.

Dr. Meissner opened by saying that he has no financial relationships with the manufacturer(s) of any commercial product(s) discussed in his presentation and that he might discuss the use of vaccines in a manner not consistent with the Package Insert, but all recommendations are in accordance with recommendations from the ACIP & AAP. He further noted that package insert reflects the inclusion and exclusion criteria used in the clinical trial data submitted by the manufacturer to the FDA; the indications in the package insert do not represent a recommendation by the FDA. If the ACIP recommendation differs from the package insert, the ACIP recommendation should be followed.

The presentation on Rotavirus vaccines and intussusception began with a review of Rotashield vaccine. RotaShield was a tetravalent rhesus-human reassortant vaccine that was licensed in August 1998. In October 1990, RotaShield was withdrawn due to association with intussusception: there was an approximately 37 fold increase in risk 3-7 days after dose 1; a smaller increase in 2nd week and 1st week after dose 2; approximately 1 excess case per 10,000 vaccinees or approximately 10 excess cases per 100,000 vaccinees. The baseline intussusception rate is estimated at 34 cases/100,000 children.

Next, RotaTeq (RV5) and Rotarix (RV1) were reviewed. RotaTeq was licensed in 2006, and contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains, with the vaccine viruses suspended in a buffer solution. Rotarix (RV1) was licensed in 2008, contains one strain of live attenuated human rotavirus (type g1p1A[8]) isolated from a child in Cincinnati, and is provided as a lyophilized powder.

Dr. Meissner posed the question: How do you decide if a vaccine is safe? He then described a Post-marketing Rotarix study in Mexico, in which it was found that the Increased relative risk of intussusception is 1.8 (99% CI 1.0-3.1) within 31 days after 1st dose. In U.S. this translates to 0-4 cases/100,000 infants after 1st dose, while the background intussusception rate in U.S. 34 cases/100,000. The Mexico study did not evaluate RotaTeq. At this time, the US experience is not large enough to determine the risk associated with RotaTeq but the risk is expected to be similar.

Further, Dr. Meissner presented the results of a study Relative Risk of Intussusception Associated With Rotavirus Vaccines in Australia's National Immunization Program.

At the June 2013, the ACIP evaluated Rotavirus vaccination and intussusception. For RV5, the attributable risk for intussusception is 1 in 67,000 to 1 in 199,000 vaccinated infants. For RV1, the attributable risk for intussusception is 1 in 19,000 vaccinated infants (one study). "Both vaccines cause a few excess cases of intussusception but this risk needs to be weighed against the benefits of hospitalizations and outpatient visits prevented." Intussusception occurs randomly in infants at 34/100,000; for comparison, approximately 1-5 extra cases intussusception/100,000 is estimated to occur among infants who receive RV1, RV5.

Dr Meissner discussed theories about the relationship between Rotavirus vaccination and intussusception. He mentioned that the mechanism of intussusception due to vaccine not understood. The period of greatest risk correlates with maximum shedding. Rotavirus vaccination may trigger early intussusception in infants who would develop intussusception later in infancy. Wild-type rotavirus infection may cause intussusception. Rates of fecal shedding of vaccine strain are lower in low income populations compared to middle and high income settings and thus the rate of intussusception may be lower. In some countries, co-administered OPV suppresses rotavirus vaccine strain replication so second rotavirus vaccine dose may have greater association with replication and immune response .

Finally, Dr. Meissner presented data on the relationship of age of administration of RotaShield Dose 1 and intussusception during 9 months of use in United States.

Dr. Meissner noted there is some evidence of a direct relationship between the older age of the subject at time of vaccine administration and the risk of intussusception. One unanswered question is whether intussusception would be less common if the vaccine were administered at an earlier age. However, at this time, rotavirus vaccine should be administered only as recommended by the ACIP and AAP.

In summary, regarding the safety of Rotavirus Vaccines: the balance of benefits and risks at a population level is highly favorable, despite varying incidence of intussusception.

Dr. Moriarty asked if there are any new data on the safety of Rotavirus vaccine and premature infants? Dr. Meissner stated the issue of vaccine administration to preterm infants is being evaluated but at this time the recommendations from the ACIP and AAP should be followed. .

Manufacturer Presentations

GlaxoSmithKline Vaccines (GSK) - Rotarix

Misha Honaker, Marketing/Commercial Strategy, GSK, presented information about GSK's Rotarix Vaccine.

Ms. Honaker mentioned that the presentation was derived from the prescribing information and referred the attendees to the prescribing information for future reference. Ms. Honaker showed slides detailing the indications, safety information and efficacy data, price and packaging information for Rotatrix, GSK's Rotavirus vaccine.

Rotatrix is indicated for prevention of rotavirus gastroenteritis (RGE).

Regarding safety and efficacy, Ms. Honaker noted that detailed information regarding clinical trials is included in the prescribing information. She also shared a summary of the European Efficacy Study, which demonstrated significant and sustained reduction in hospitalization through 2 rotavirus seasons. In addition, there is demonstrated efficacy after 1 dose of Rotarix vaccine, which is serotype specific (G1, 3, 4 and 9) against severe RGE.

Ms. Honaker stated that the adverse event profile was comparable to placebo.

Price and packaging – Ms. Honaker referred to Dr. Lett's table, which notes that Rotarix is a 2-dose series with a cost of $184.30 for the series. The packaging was shown; Rotarix comes as a 10 pack of lyophilized vaccine.

The recommended dose and schedule aligns with ACIP recommendations and the pediatric routine immunization schedule. The Rotarix schedule aligns with the 2 and 4 month well baby visits. Also, the series can be started as late at 20 weeks in order to be completed by 24 weeks. Rotarix is a 1 mL dose to be delivered orally between 6 and 24 weeks of age.

Ms. Honaker gave a demonstration of vaccine administration, showing that one attaches the transfer adaptor to the vial, attaches the oral applicator, mixes, pulls out the applicator and it's ready to administer. The vaccine must be used within 24 hours of mixing. It is a 1 mL, controlled administration.

A question was asked about the applicator containing lates, to which Ms. Honaker responded that there is no latex in the rubber plunger; the latex is in the tip of the cap, and the latex would not come into contact with the baby.

Ms. Honaker reinforced that that the vaccine should only be mixed with the diluent that is provided. The lyophilized vaccine must be stored in the refrigerator and used 24 hours post-mixing.

Ms. Honaker noted some advantages of the Rotarix vaccine as having significant efficacy; adverse events profile similar to placebo; only a 2 dose series; a flexible dosing schedule that helps avoid missed opportunities, especially for older babies.

<u>Questions/Comments</u>

Dr. Moriarty commented that it would be helpful if the package insert included more specific information on latex, specifically, that it is in the cap and that latex is used within the processing facility.

<u>Merck Vaccines (RotaTeq)</u>

Dr. Barbara Homeier, Regional Medical Director, Merck Vaccines, presented information about the Merck Rotavirus vaccine, RotaTeq. She also noted that she is a pediatrician herself.

Dr. Homeier noted that she would be discussing why we vaccinate; the epidemiology of rotavirus gastroenteritis; how Rotateq is designed; and clinical studies on safety and efficacy.

In the pre-vaccine Era, rotavirus accounted for 5%–10% of all gastroenteritis episodes among children less than 5 years of age. Rotavirus gastroenteritis (RGE) was the most common cause of severe diarrhea and accounted for a higher proportion of severe episodes leading to clinic or hospital visits (accounted for 30%–50% of all hospitalizations for gastroenteritis among children less than 5 years of age). The estimated burden of RGE disease in US children <5 years of age before rotavirus vaccine was presented, including an estimated total of 2.7 million symptomatic episodes per year, and a cumulative risk by age 5 of 4:5 to experience symptomatic episodes and 1:14 to experience hospitalization. The spectrum of symptoms can range from asymptomatic infection to severe dehydration, with children aged 4–23 months accounting for the majority of severe RGE. However, there is no reliable way to predict the course of disease or severity of symptoms, multiple infections can occur, and subsequent infections are generally less severe than first infections. Dr. Homeier showed a slide on Natural Rotavirus Infection: Cumulative Probability by 24 Months of Age, noting that ~40% of children had at least 3 rotavirus infections by age 2 years.

Dr. Homeier presented a slide demonstrating the wheel structure of rotavirus, and then a map of US cities with laboratory sites that participated in the National Rotavirus Strain Surveillance System (NRSSS) from 2005–2008. The surveillance study looked at the distribution of G serotypes in the United States from2005–2008. There was both geographic and temporal variation in serotypes, and, in summary, multiple serotypes can cause RGE.

RotaTeq Indication and Dosing - RotaTeq is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks. The vaccination series consists of 3 ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age.

Safety Information - RotaTeq should not be administered to infants with a demonstrated history of hypersensitivity to the vaccine or any component of the vaccine. Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive RotaTeq. Post-marketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered RotaTeq and later identified as having SCID. Infants with a history of intussusception should not receive RotaTeq.

RotaTeq is an oral pentavalent vaccine suspended in a buffered stabilizer solution. It may be administered directly from the tube. RotaTeq contains 5 human-bovine reassortants: G serotypes - human G1, G2, G3, G4, and bovine G6; and P serotypes – human P1A[8] and bovine P7[5].

RotaTeq provides early exposure at the 2-, 4-, and 6-month well-baby visits to multiple serotypes (G1, G2, G3, and G4) that commonly cause RGE. Serotypes G1, G2, G3, and G4 represented 88% of rotavirus infections in the United States from 2005 to 2008. Overall, G2 historically has been the second most common serotype (following G1) found in the United States, although rotavirus serotype distribution has varied by region and year. Dr. Homeier noted that the exact immunologic mechanism by which rotavirus vaccines protect against rotavirus gastroenteritis is unknown.

Dr. Homeier described the Rotavirus Efficacy and Safety Trial (REST), in which 68,038 subjects were evaluated in 11 countries. The study showed 98% efficacy against severe RGE and 74% efficacy against any severity of RGE through the first rotavirus season after vaccination. Up to 2 years after vaccination there was an approximately 95% reduction in combined incidence of hospitalizations/ED visits for RGE.

The REST also looked at intussusception data. The data did not suggest an increased risk of intussusception relative to placebo.

Selected safety information was shared from the REST, Phase III studies, and the Postmarketing Observational Safety Surveillance Study (PRISM). In summary, Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient contacts. In clinical trials, the most common adverse events included diarrhea, vomiting, irritability, otitis media, nasopharyngitis, and bronchospasm. In post-marketing experience, intussusception (including death) and Kawasaki disease have been reported in infants who have received RotaTeq. RotaTeq may not protect all vaccine recipients against rotavirus. RotaTeq provides efficacy against common circulating rotaviruses (G1, G2, G3, G4), demonstrated a high level of protection in clinical studies, and has a safety profile demonstrated through clinical trials.

Dr. Homeier reminded participants to please read the prescribing information available at this presentation. In addition, she stated that Merck Vaccines is supportive of vaccine choice at the provider level.

Discussion

Dr. Palfrey asked the group to consider whether there is an advantage to having 2 slightly different vaccines used in Massachusetts in order to promote herd immunity.

Deliberation and Voting

Council members deliberated on the following:

Does the Council recommend:

- Maintaining current DPH policy of exclusively supplying RotaTeq (Merck vaccine);
- Changing DPH policy to exclusively supply Rotarix (GSK vaccine);
- Changing DPH policy to allow for provider choice on rotavirus vaccines?

Rotavirus Vaccine Discussion

Dr. Samuels asked what the budget impact would be if patients were switching practices and stared a series in one office and needed to finish a series through another office that supplied a different formulation? Mr. Talebian replied that it would be hard to predict, but that MDPH does not anticipate a large number of providers switching formulations, at least initially. This has been what MDPH has observed with the offering of choice for vaccine formulation thus far. Dr. Adler mentioned that while patients do tend to move practices, they see less of that during the 2-4-6 month early well child time frame.

Dr. Norton asked about the outer age limit for the administration of Rotarix vaccine. Dr. Lett confirmed that the ACIP maximum recommended age for first dose is 14 weeks and 6 days, not 24 weeks as stated by the manufacturer.

Dr. Lett also mentioned that Massachusetts has lower immunization rates for Rotavirus than other childhood vaccines, and that the 2 dose series might encourage completion.

Dr. Kruskal noted that while safety and efficacy are comparable, there are the number of doses in the series as well as the reconstitution factors to consider. These two factors seem to balance each other out in weighing whether or not to allow choice. Dr. Moriarty noted that the other vaccines that were reviewed by the committee have been interchangeable and this one is not. However, he said it would be good to have a formulation that could be started later. Dr. Lett confirmed again that the ACIP maximum recommended age for first dose is 14 weeks and 6 days, not 24 weeks as stated by the manufacturer. She also stated that in the past when the MDPH has had to change formulations due to shortage or another reason, the manufacturers have partnered to provide education at the provider office level.

Dr. Palfrey mentioned that in previous meetings it had been stated that allowing choice would mean more visits from vaccine representatives in provider offices. He asked if anyone had noticed this to be true after the recent decisions to offer choice for other vaccines? No one said that they found it to be true. Dr. Palfrey commended the represented manufacturers for this, and asked that the trend of not adding additional visits to providers be continued.

Dr. Samuels stated that he was going to need to leave shortly, and while he is concerned about the long term budget impact, he would support rotavirus vaccine choice. Mr. Talebian clarified that the Committee would be making a recommendation to the Department; however, if the budget impact was too severe the MDPH can decide to not integrate the recommendation.

Dr. Kruskal voiced a concern over large numbers of children changing practices potentially due to external factors and the need to be able to track doses received from different series. Dr. Samuels noted the immunization registry would help with that.

After discussion, the Council recommended that MDPH allow choice for rotavirus vaccine.

Finally, there was a question about the status of the MIIS, and Ms. English gave an update. In addition, up-to-date information can always be found at www.contactmiis.info.

Mr. Talebian directed attendees to the meeting schedule listed on the agenda for future meetings:

January 16, 2014
April 17, 2014
July 17, 2014
October 16, 2014
January 15, 2015
April 16, 2015
July 16, 2015
October 15, 2015

The meeting was adjourned.