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WHAT'S NEWS

Give **Tdap vaccine to pregnant women** to prevent pertussis in both the women and their newborns, ACIP recommends. **2**

This summer watch out for foodborne illnesses, Dr. Stephen I. Pelton warns in the **ID Consult** column. **4**

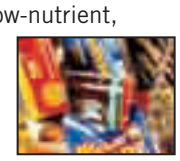
Help **helicopter parents stop hovering** with Dr. Barbara J. Howard's help in the **Behavioral Consult** column. **8**

Pediatricians are essential when **cystic fibrosis patients live far from a CF center**, Dr. Lucille A. Lester explains in **Subspecialist Consult**. **12**

Dr. Kevin T. Powell discusses how medicine needs to improve the **informed consent** process in the **Beyond the White Coat** column. **14**

The **Passport to Pediatrics** column highlights a new program in Haiti that provides books at the 4- to 6-month well-child visit. **18**

Eating too many low-nutrient, high-fat snacks was **one of three modifiable risk factors for obesity** identified in a recent study of low-income children. **18**



After a long debate, the **AMA backs an individual mandate for health insurance**, among other resolutions. **20**

ACIP: Menactra OK for Some High-Risk Infants

The committee opted to postpone voting on whether to include infants with functional or anatomic asplenia.

BY HEIDI SPLETE

FROM A MEETING OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION'S ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

ATLANTA – The meningococcal vaccine MCV4-D (Menactra) is now recommended for use in certain subgroups of high-risk children aged 9-23 months, ACIP voted at its June meeting.

Dr. Amanda Cohn of the CDC's meningitis and vaccine preventable disease branch noted that the recommendations involve a very small subset of the population, and that they do not apply to this age group in general.

ACIP voted that specific groups of children aged 9-23 months at increased risk for meningococcal disease receive a two-dose series of MCV4-D taken 3 months apart:

- Infants needing protection prior to traveling or moving to an area where meningococcal disease is epidemic or highly endemic. Travelers can receive their two doses 2 months apart to accommodate travel schedules.
- Infants with complement component

See **High-Risk Infants** *page 6*

HEIDI SPLETE/ELSEVIER GLOBAL MEDICAL NEWS

Dr. Amanda Cohn of the CDC's meningitis and vaccine preventable disease branch noted that the recommendations involve a very small subset of the population, and that they do not apply to this age group of 9-23 months in general.

Benefit Outweighs Rotavirus Vaccine's Risk of Intussusception

The experience in Mexico may not apply to developing countries, most of which use the OPV.

BY MARY ANN MOON

FROM THE NEW ENGLAND JOURNAL OF MEDICINE

The second-generation rotavirus vaccine appears to raise the risk of intussusception in a similar manner as its predecessor, but its benefits still far outweigh that risk, according to a recent report.

Case series and case-control analyses of immunization data from Mexico and Brazil indicate that the short-term risk of intussusception is approximately 1 in every 51,000-68,000 infants receiving the rotavirus vaccine (RV1, Rotarix), which translates to an annual "excess of 96 hospitalizations … and 5 deaths in the two countries combined."

This risk is far exceeded by "the real-world benefits of RV1 vaccination, which has annually prevented more than 80,000 hospitalizations and 1,300 deaths in Mexico and Brazil," said Dr. Manish M. Patel of the Centers for Disease Control and Prevention, Atlanta, and his associates.

"These emerging data on safety and benefits have been reviewed by the World Health Organization as well as by regulatory agencies and immunization advisory committees in Brazil, Mexico, and the United States. … [T]hese groups unanimously favored continuing the recommendation that rotavirus vaccination be administered to infants to prevent severe and potentially fatal rotavirus disease," the investigators noted (N. Engl. J. Med. 2011;364:2283-92).

They undertook this study because, after Brazil and Mexico added RV1 to their national childhood immunization programs in 2007, "the combined

See **Rotavirus** *page 6*

Some Concerns Persist

High-Risk Infants *from page 1*

deficiencies such as C3, C5-9, properdin, factor H, and factor D deficiencies.

► Infants in a defined risk group for a community or institutional outbreak.

► Infants with HIV, if another indication for vaccination exists.

The committee, however, opted to postpone voting on whether infants aged 9-23 months with functional or anatomic asplenia, including those with sickle cell anemia, should receive the MCV4-D vaccine.

"This will be on the agenda to consider at a future time when more information becomes available," said Dr. Carol Baker, ACIP chair and professor of pediatrics at Baylor College of Medicine, Houston. "We are not just a rubber stamp for the FDA licensing."

ACIP also voted unanimously to include the recommendations in the Vaccines for Children Program.

The indication for MCV4-D as a two-dose primary series for infants aged 9-23 months was approved by the U.S. Food and Drug Administration in March 2011, Dr. Cohn said. "This is the first meningococcal vaccine licensed in children under 24 months, but others are likely to be available within the year." Prelicensure safety data met noninferiority criteria, with no serious adverse events, and postlicensure safety surveillance will be conducted for children through age 23 months.

The recommendations were based on immunogenicity and safety data presented by Dr. David R. Johnson of Sanofi Pasteur, manufacturer of Menactra. He presented several phase III studies that included immunogenicity data from 1,561 infants and safety data from 3,267 infants.

In one study of 147 children, the protective response rates after two doses of MCV4-D (defined as the percent achieving serum bactericidal assay with human complement [SBA-HC] immune titers of at least a ratio of 1:8) against meningococcal serogroups A, C, Y, and W-135 were 91%, 100%, 95%, and 82%, respectively, Dr. Johnson said. Seroprotection rates when MCV4-D was given with MMRV (measles, mumps, rubella, varicella) were higher than when PCV7 was given with MMRV. However, pneumococcal geometric mean concentrations when PVC7 was given with MCV4-D were lower than with PCV7 given with MMRV.

The impact of MCV4-D on the effectiveness of the pneumococcal vaccine was cause for concern. "We don't want to do anything to impact the burden of pneumococcal disease in the high-risk patients" Dr. Michael Brady, chair of the American Academy of Pediatrics committee on infectious disease, said during the discussion period prior to voting. He also is chair of the department of pediatrics at Ohio State University in Columbus.

Many ACIP members expressed similar concerns about the risks of interference that could occur with the coadministration of a pneumococcal vaccine and meningococcal vaccine in the specific subset of children with functional or anatomic asplenia, including sickle cell anemia, and the vote was postponed based on these concerns. The rate of medically significant adverse events from 30 days to 6 months after MCV4-D plus concomitant vaccines was less than 5%. No data were presented on safety or immunogenicity data for MCV4-D and PCV13.

Dr. Cohn had no relevant financial disclosures. ■

First Week After First Dose

Rotavirus *from page 1*

annual birth cohort of approximately 6 million in these two countries provided an opportunity to assess whether routine vaccination with RV1 was associated with intussusception," Dr. Patel and his colleagues wrote.

Using hospital records, they identified 615 infants who developed intussusception (285 in Mexico and 330 in Brazil) and matched them with 2,050 control infants (739 in Mexico and 1,311 in Brazil). Of these, 594 case patients (97%) and 2,033 controls (99%) had a history of vaccination confirmed by a vaccination card.

In Mexico, intussusception was significantly more likely to develop in the first week after the first dose of the vaccine than during other periods, with an incidence ratio of 5.3.

"This corresponds to the dose and period in which there is peak intestinal replication of vaccine virus and in which a local inflammatory response in the lymphatic tissue or intestines may occur – a response that has been implicated in the pathogenesis of intussusception," the investigators said.

In contrast, "neither a clustering of cases after the first dose nor a risk of the magnitude noted in Mexico was observed in Brazil. However, a small but significantly elevated rate was noted 1-7 days after the second dose," they said.

This absence of risk with the first RV1 dose was at first "perplexing." However, RV1 is administered together with oral poliovirus vaccine in Brazil but with inactivated poliovirus vaccine in Mexico. The first dose of oral polio vaccine is known to decrease the immunogenicity of RV1 when the two are given together, which may in turn reduce the risk of RV1-associated intussusception.

"Other factors, such as differences in the diets of the infants, breastfeeding practices, the natural risk of intussusception, and maternal antibody levels, might also have contributed to the variation in risk between Mexico and Brazil," Dr. Patel and his associates wrote.

"Our benefit-risk analysis indicated that an RV1 vaccination program would avert 663 deaths and 11,551 hospitalizations due to rotavirus disease in Mexico and 640 deaths and 69,572 hospitalizations in Brazil among children younger than 5 years of age.

"In contrast, we predict that a vaccination program would cause 41 excess hospitalizations (approximately 1 per 51,000 vaccinated infants) and 2 deaths due to intussusception in Mexico and 55 excess hospitalizations (approximately 1 per 68,000 vaccinated infants) and 3 deaths in Brazil," the researchers said.

They emphasized that the experience in Mexico may not apply to developing countries, most of which use the oral poliovirus vaccine (OPV). Also, the immune response to rotavirus vaccination, as well as fecal shedding of vaccine strains of the virus, are generally lower in developing than in industrialized countries, which may indicate a difference in intussusception risk.

This study was funded in part by the GAVI Alliance under a collaborative agreement with the Program for Appropriate Technology in Health (PATH) and in part by the U.S. Department of Health and Human Services. Rotarix is a product of GlaxoSmithKline. Dr. Patel and his coinvestigators reported no relevant financial disclosures. ■

VIEW ON THE NEWS

The Bottom Line

In an article that is a must-read for all of us providing pediatric immunizations, Dr. Patel and his associates detail a risk-benefit analysis of rotavirus vaccine and the potential link to intussusception based on data from Mexico and Brazil.

This case-control study estimates the risk of intussusception to be 1 per 51,000 infants in Mexico in the 7 days following the first dose and 1 per 68,000 infants in Brazil in the week following the second dose.

Is this potential risk scientifically plausible?

And what is the bottom line?

The timing of the intussusception cases following the first dose of RV1 in Mexico corresponds to the time of greatest replication of vaccine virus and of gut inflammatory response (likely enlargement of submucosal lymph nodes as potential leading edges) – both known to predispose to intussusception.

An Australian report also suggested a similar temporal risk of intussusception in the week following the first dose of either RV1 or RV5.

Interestingly, in Brazil, the intussusception risk is noted after the second dose – but not the first – and this is more difficult to explain.

The authors suggest that oral polio vaccine, which is coadministered with RV1, results in significant replication of polio vaccine virus, a decrease in the gut inflammatory response, and a decrease in the replication of rotavirus vaccine virus.

This is consistent with data from South Africa, where seroconversion after dose 1 of RV1 is 13% in those receiving concurrent live polio vaccine and 33% in those who receive inactivated polio vaccine.

Dr. Patel and his associates suggest that, in Brazil, the second dose is essentially like the first dose in places where killed vaccine is used: that is, associated with the dose when greatest replication of rotavirus vaccine virus occurs.

The bottom line? The benefit from rotavirus vaccine is impressive – RV1 prevented 80,000 hospitalizations and 1,300 deaths from diarrhea annually in these two countries.

The authors point out that this translates in Mexico to rotavirus vaccine prevention of 663 child deaths and 11,551 hospitalizations while causing 2 excess deaths and 41 excess hospitalizations from intussusception above baseline.

There may be more – other studies hint that the absolute risk of intussusception at a later age may be reduced in children who have received rotavirus vaccine.

In my institution, hospital admissions for rotavirus infection have been uncommon in the last 3 years such that few of our nearly 100 pediatric house-staff have ever cared for a child who has been hospitalized with rotavirus infection.

The efficacy of vaccine and subsequent benefits of rotavirus immunization have been increasingly well documented throughout the world.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has reviewed the data from this report, and the committee unanimously recommended the continuation of current U.S. policy, and reminded practitioners of the importance of discussing risk/benefit issues for all vaccines.

As pediatric providers,education of parents and vigilance in noting and reporting any vaccine adverse events remain key components of our work.

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