Intussusception, Infection, and Immunization: Summary of a Workshop on Rotavirus

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ABSTRACT. This article summarizes the proceedings of a workshop sponsored by the National Institutes of Health and the National Vaccine Program Office, and held in Bethesda, Maryland, on January 21, 2000. The objective of the meeting was to focus research toward an understanding of the basis for the possible association between intussusception and the reassortant rhesus-human rotavirus vaccine tetravalent (RRV-TV). After numerous reports of intussusception after administration of RRV-TV, the manufacturers of this vaccine voluntarily withdrew it from the United States market. The American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians also withdrew their original recommendations for administration of RRV-TV to children at 2, 4, and 6 months of age. These actions will have global implications for the prevention of morbidity and mortality attributable to rotavirus infection. Benefit-cost ratios for the use of RRV-TV will be substantially different in developing countries compared with developed countries. Therefore, extensive research is needed in both of these settings, to further our understanding of the epidemiology, pathogenesis, and pathology of both rotavirus disease and intussusception to enable optimal prevention. The workshop reviewed the current understanding of the possible association between RRV-TV and intussusception, as well as the possible association between a variety of viral infections and intussusception. The workshop also identified critical areas of research regarding this possible association. This research will be essential not only for the development of safe and effective rotavirus vaccines, but for the development of other oral vaccines as well. Pediatrics 2001;108(2). URL: http://www.pediatrics.org/cgi/content/full/108/2/e37; rotavirus, intussusception, rhesus rotavirus vaccine tetravalent, workshop.

ABBREVIATIONS. RRV-TV, rhesus-human reassortant rotavirus vaccine-tetravalent; AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; VAERS, Vaccine Adverse Events Reporting System; CDC, Centers for Disease Control and Prevention; GI, gastrointestinal; CI, confidence interval; HMO, health maintenance organizations; NSP, nonstructural protein.

On August 31, 1998, the US Food and Drug Administration licensed RotaShield—a live, orally administrated, rhesus-human reassortant rotavirus vaccine-tetravalent (RRV-TV) manufactured by Wyeth Laboratories. The vaccine was subsequently recommended by the American Academy of Pediatrics (AAP), the Advisory Committee on Immunization Practices (ACIP), and the American Academy of Family Physicians for routine administration to children at 2, 4, and 6 months of age in the United States.

In the prelicensure trials of RRV-TV, 5 cases of intussusception occurred among the 10,054 infants who received vaccine, and 1 case occurred among the 4,633 recipients of placebo. This difference was not statistically significant, but intussusception was included in the manufacturer's product insert and in the published recommendations of the ACIP and AAP.1 During the postlicensure evaluation period, numerous reports of intussusception after administration of RRV-TV were received through the Vaccine Adverse Events Reporting System (VAERS). VAERS is operated jointly by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration.2,3 As a result, immunization with the RRV-TV was suspended.3 In October 1999, the vaccine manufacturer voluntarily removed the vaccine from the market. After careful review of all available data that demonstrated a possible association between RRV-TV and intussusception, the AAP, ACIP, and American Academy of Family Physicians withdrew their recommendations for use of the vaccine.4,5 These findings and consequent changes in recommendations have global implications for the prevention of morbidity and mortality attributable to rotavirus infections.

On January 21, 2000, the National Institutes of Health and the National Vaccine Program Office convened a workshop to focus research toward an understanding of the basis for the possible association between intussusception and RRV-TV. The principal objectives of this workshop were: 1) to identify the relevant knowledge gaps pertaining to the epidemiology, pathology, and pathogenesis of intussusception, particularly as they relate to gastrointestinal (GI) tract infections and rotavirus immunizations; and 2) to define a research agenda that will address these gaps, enabling progress toward safe and effective rotavirus infection prevention strategies. This report summarizes the information presented at the
workshop, with speakers cited where appropriate, as well as the discussion that occurred.

**ROTAVIRUS**

Rotavirus is the most common cause of severe gastroenteritis in infants and children <5 years old. Rotavirus gastroenteritis is characterized by watery diarrhea usually preceded or accompanied by vomiting and fever. Rotavirus infection can be fatal as a result of severe dehydration, electrolyte loss, and acidosis.6

In most developing countries, rotavirus gastroenteritis occurs year round, and is a major cause of morbidity and mortality. Between 20% and 70% of diarrheal illness that results in hospitalization of young children is caused by this pathogen. An estimated 600 000 to 800 000 deaths occur annually as a result of rotavirus-associated illness; this represents 20% to 27% of the 3 million annual deaths from diarrhea. In developing countries, diarrheal disease prevention strategies, such as improving water quality, food handling, and sanitation practices, have had minimal impact on disease associated with rotavirus. The primary intervention strategy to prevent mortality in these countries has been the use of oral rehydration therapy. Although effective in preventing deaths from dehydration, oral rehydration is not a mechanism for primary prevention of rotavirus-associated illness.5,7

In the United States, rotavirus infection occurs predominantly in the winter and spring months (November to May). Approximately 2.7 million children under 5 years of age experience diarrheal episodes attributable to rotavirus annually; this accounts for 5% to 10% of all diarrheal disease in this age group. Virtually all children experience a rotavirus infection by 3 years of age, and reinfection is common. Rotavirus illness in the United States is associated with 500 000 physician visits and 50 000 hospitalizations annually; an estimated 20 to 40 deaths also occur each year.6–8

Rotavirus-associated illness is responsible for considerable medical and societal costs; an affordable, effective, and safe rotavirus vaccine would be an important means of reducing the substantial morbidity and mortality caused by this pathogen.

**INTUSSUSCEPTION**

Intussusception is the most common cause of intestinal obstruction in infants and children <2 years old. Intussusception occurs when a proximal portion (intussusceptum) of the bowel telescopes into a distal portion (intussusciens); ileocolic (ileum telescoped into the colon) intussusception is the most common form of this condition in infants and young children. This telescoping or invagination of the bowel often leads to edema and compression of the mesenteric blood vessels. Venous congestion and ischemia of the intestinal mucosa may cause bleeding and an outpouring of mucous into the lumen of the intestine, which results in production of the characteristic “red currant jelly stool.” Progression of the process may result in arterial obstruction, necrosis, perforation of the bowel, and possibly death.9–12

Intussusception is known to result from several pathologic lead points including Meckel’s diverticulum, duplication cysts, polyps, hematomas, and lymphomas.9 However, 90% of all cases of intussusception that occur in children are described as idiopathic. These idiopathic cases are believed to arise from hypertrophy of infected lymph nodes, including Peyer’s patches. To date, intussusception has been associated most frequently with respiratory or GI tract infections, particularly those resulting from adenovirus and enterovirus.10,11 The hypertrophied lymph node masses associated with these infections are believed to form the lead point that initiates the chain of events that result in intussusception.12

In the United States, idiopathic intussusception occurs primarily in children younger than 2 years of age13 and males are affected approximately 3 times more frequently than females.14 The background rate of intussusception in the United States is estimated to be approximately 50 cases per 100 000 infant-years2 with the highest incidence occurring between the ages of 3 and 9 months. In contrast with rotavirus gastroenteritis, intussusception lacks distinct seasonal peaks.15 Limited data are available on the epidemiology of intussusception in developing countries. An investigation of intussusception conducted in Lima, Peru, and presented at this workshop by Dr Claudio Lanata (Instituto de Investigacion Nutricional, Peru), estimates the incidence rate to be about 12 to 13 per 100 000 in children <1 year old. These data are difficult to compare to those from the United States, and additional studies will be required to obtain more accurate baseline rates of intussusception for the United States, as well as developing countries.

Radiographic and sonographic techniques are highly sensitive and specific for establishing the diagnosis of intussusception. If identified within the first 24 hours, approximately 75% of cases can be reduced effectively with air or contrast enemas. Although once the primary mode of therapy in the United States, surgical reduction is now required in only a minority of cases, and resection is rarely necessary,9,13 particularly when diagnosed early. In developing countries where diagnostic and treatment capabilities are limited, death is thought to be a more common outcome.16

**STUDIES PRESENTED**

**Epidemiology: Association of Intussusception With Wild-Type Rotavirus and RRV-TV**

**VAERS Data**

As of December 1999, 99 cases of intussusception after receipt of RRV-TV had been reported to VAERS. Of these cases, 60 (61%) had onset within 7 days of receipt of RRV-TV; 49 (82%), 10 (17%), and 1 (1%) of these cases occurred after the first, second, and third dose of RRV-TV, respectively. Of the 60 cases with onset within 7 days of receipt of RRV-TV, 32 (53%) underwent surgery, 7 (12%) required bowel resection, and 1 child died. The reasons for the high rate of surgical intervention and bowel resection are...
not clear, but may be related to the young age of presentation. Of the 99 cases, 86 (87%) had received other vaccines in addition to RRV-TV at the same visit.

In June 1999, in response to the first reports received by VAERS, the CDC initiated a matched case-control study in 19 states. The objective of this study was to estimate the relative risk of intussusception among infants immunized with RRV-TV compared with those not receiving the vaccine. Approximately 1.8 million doses of vaccine had been distributed nationwide as of June 1999; this investigation was conducted in geographic regions where 80% of the vaccine had been distributed. The study included >400 children with intussusception and >1600 children in total. Analysis of the preliminary data, as presented by Dr Trudy Murphy (National Immunization Program, CDC), showed that children who received RRV-TV were significantly more likely to develop intussusception (odds ratio: 1.8) than those who did not receive the vaccine. The risk was greatest during the 3 to 7 day period after immunization with the first dose (odds ratio: 25; 95% confidence interval [CI]: 9.5–65.1; \( P = .0001 \)). Risk did not vary significantly by age at first dose. The odds ratios for intussusception within the highest risk window (3–7 days) after immunization with dose 1 among the different age groups were as follows: 28.1 (95% CI: 3.0–264.7) for children 1 to 2 months of age; 20.6 (95% CI: 6.0–71) for children between 3 and 5 months of age; and 31.4 (95% CI: 3.9–250.4) among children 6 to 8 months of age.

Vaccine Safety Datalink Cohort Study Data

A population-based cohort study was also conducted. Data were obtained from the Northern and Southern California Kaiser Permanente Health Maintenance Organizations (HMOs), which are part of CDC’s Vaccine Safety Datalink—a partnership of 4 HMOs established for ongoing postlicensure surveillance for vaccine safety evaluation. The study also included data from 8 additional HMOs that had offered RRV-TV to their participants. The preliminary results of the cohort study, presented by Dr Piotr Kramarz (National Immunization Program, CDC), were similar to those of the matched case-control study. In the final analysis, the investigators estimated 1 vaccine-attributable case of intussusception per 5000 to 10 000 infants vaccinated with RRV-TV. These calculations were based on a predictive model of a fully implemented national program of vaccination (cohort 3.8 million infants with 90% RRV-TV vaccination rate).

Other Data

Two additional studies have examined the possible association between naturally occurring rotavirus infection and intussusception. In the first study, presented by Dr Emily Chang (Harbor—University of California, Los Angeles Medical Center), it was found that among children under 3 years of age who had not been immunized with RRV-TV, none of the 480 children who had laboratory confirmed rotavirus diarrhea between November 1997 and July 1999 developed intussusception. Likewise, none of the 122 children who had intussusception between October 1992 and November 1999 showed evidence of recent rotavirus-associated illness. When the seasonality and age distribution of the 2 diseases among these unvaccinated cohorts were analyzed, the peak age for wild-type rotavirus infection was between 6 and 17 months, with a distinct seasonal peak between December and February. In contrast, the incidence of intussusception was greatest between the ages of 4 and 9 months, and there was no distinct seasonal peak. In the second study, presented by Dr Margaret Rennels (University of Maryland School of Medicine, Baltimore, Maryland), hospital discharge data for children <3 years old with either intussusception or rotavirus infection in the State of New York between 1993 and 1995 had been collected. The occurrence of intussusception was distributed evenly throughout the year, but the pattern for rotavirus gastroenteritis was distinctly seasonal, peaking in late winter and early spring. The data from both of these studies suggest that wild-type rotavirus infection is not a principal cause of intussusception.

Although prelicensure safety and efficacy evaluation trials of RRV-TV had been conducted in Finland, Sweden, Venezuela, and the United States, at the time RRV-TV was withdrawn from the United States market, RRV-TV had been licensed only in the United States; postlicensure data from other countries are, therefore, not available. This vaccine is currently not being used anywhere in the world.

Pathology of Intussusception Associated With RRV-TV

Pathology specimens from 13 cases of intussusception that had occurred after receipt of RRV-TV are being investigated at CDC in collaboration with other institutions. Dr Joseph Bresee (Respiratory and Enteric Virus Branch, CDC, Atlanta, Georgia), and Dr Wun-Ju Shieh (Division of Viral and Rickettsial Diseases, CDC) presented preliminary results of the investigations. The quantities and anatomic locations of the specimens that have been collected are highly variable (intestinal, appendices, mesenteric lymph nodes, etc).

Children, from whom the specimens were obtained, ranged in age from 3 to 6 months; the median age was 4 months. The interval from date of immunization to development of intussusception ranged from <8 days to >2 weeks. The gross pathology of the tissue specimens shows ileal and ileocecal hyperemia and edema; 11 (85%) of the 13 cases were idiopathic. A duplication cyst and a Meckel’s diverticulum were identified in the other 2 cases, respectively. Microscopic examination of all specimens revealed mucosal and submucosal hemorrhage and necrosis; some vascular congestion and lymphoid hyperplasia were also noted.

In an effort to identify markers of RRV-TV association with intussusception, specimens from children with intussusception who had received RRV-TV will be compared with bowel tissue from children with intussusception who had not received RRV-TV, as well as to bowel tissue from children who have undergone surgery for conditions other than intussu-
Pathogenesis of Intussusception and Rotavirus Infections

The pathogenesis of idiopathic intussusception in humans is still poorly understood, and current models have not helped to further our understanding of this process. Although naturally occurring intussusception has been reported in a number of animals including cattle, horses, dogs, and pigs, intussusception in animals is so uncommon that the causes and risk factors are largely unknown. No data on intussusception in the rhesus monkey were presented or discussed at the workshop. There is the suggestion in the veterinary literature that any of a variety of infections may be a risk factor. However, as in humans, the cause of intussusception in animals seems to be multifactorial.

As discussed by Dr Mary Estes (Baylor College of Medicine, Houston, TX), experimental models for wild-type rotavirus infection have been developed in several animals including pigs, sheep, cows, rabbits, mice, and rats, and have been helpful in furthering our understanding of the pathogenesis of rotavirus infection in humans. Each of these animal models has advantages and disadvantages. Of the large animal models, the progression of rotavirus disease in pigs probably most closely mimics that in humans; pigs, however, are difficult to work with and expensive. Of small animals, the mouse model is particularly attractive because of the considerable body of knowledge about mouse genetics and the variety of experiments that can be performed with mice of different genetic backgrounds. In contrast to human infants who are susceptible to recurrent infections with different serotypes of rotavirus, most animals are susceptible to a single homologous serotype of rotavirus with a single infection producing life-long immunity. The suckling rat model is particularly attractive because suckling rats are susceptible to a wide range of human, bovine, rhesus, and simian strains of rotavirus. They also remain susceptible to reinfection with a different serotype of rotavirus, including human rotavirus. The suckling rats all develop diarrhea, shed viral antigen for 6 to 10 days, and have a good serologic response. The physiology of the rat’s GI tract has been extensively studied and the size of the rat has some advantages, particularly when abdominal ultrasonography is done.

Dr Estes also presented information about intussusception observed in piglets 72 hours after inoculation with porcine rotavirus. However, these findings have not been reproducible and there is currently no animal model for intussusception associated with rotavirus vaccination. In addition, there has been a licensed oral rotavirus vaccine for use in calves since 1972 and for use in young pigs since about 1978 with no direct association between the use of either of these vaccines and the occurrence of intussusception.

Data presented by Dr Menachem Hanani (Hadassah Hospital, Jerusalem, Israel) showed that intussusception can be induced experimentally in about 20% to 30% of adult mice 6 to 12 hours after injecting bacterial lipopolysaccharide endotoxin into their peritoneal cavities. No evidence of inflammation, lymphoid hyperplasia or hypertrophy, or other histopathology was apparent in the mice that developed intussusception, suggesting that the intussusception was caused by a disturbance of GI tract motility. Lipopolysaccharides can slow intestinal motility presumably through induction of the synthesis of various inflammatory agents such as prostaglandins, cytokines, and nitric oxide. When Hanani treated the mice with agents that could block the synthesis of these inflammatory mediators, the ability of the lipopolysaccharide injections to produce intussusception was reduced or eliminated. Natural rotavirus infections have been shown to increase the synthesis of prostaglandins and cytokines. These findings suggest that intussusception can occur as a result of disturbances of intestinal motility in the absence of a lead point produced by a specific lesion.

If infection with wild-type or vaccine strains of rotavirus is associated with an increased risk of intussusception, a specific component of the virus, perhaps in association with specific host factors, may be responsible. Rotavirus contains 11 genes that code for 6 structural proteins (VP1–VP4, VP6, and VP7) and 5 nonstructural proteins (NSPs). The toxic nature of NSP4 and the antigenic properties of VP4 and VP7 rank these proteins high on the list of possible viral factors hypothesized to be involved in the development of intussusception attributable to an interaction with specific yet unknown host factors. NSP4 is an endoplasmic reticulum transmembrane glycoprotein. Studies at the cellular level suggest that the C-terminal region of NSP4 acts as an intracellular receptor for the rotavirus double-layered particle, which is a requisite intermediate in virus assembly. During viral morphogenesis, the C-terminal tail of NSP4 transfers double-layered particles into the endoplasmic reticulum, where VP4 and VP7 coalesce onto these particles to form mature triple-layered virion progeny. Studies with NSP4 protein in neonatal mice and rats suggest that a domain in the C-terminal region acts as an enterotoxin. In attenuated human rotaviruses, mutations in NSP4 are limited to its N-terminal region. These observations suggest that even when a human rotavirus is attenuated, the
C-terminal toxic region of NSP4 seems to escape mutations and retains its enterotoxic potential. In addition to this conserved NSP4 domain, virulent and attenuated viruses also have a variable domain adjacent to the enterotoxic domain. The specific pathogenic process initiated by the rotavirus infection may be determined by the interaction of a specific host factor with the NSP4 enterotoxin and/or variable domain. In the extreme case, this interaction with either wild-type or vaccine strains could lead to intussusception.

Individuals also may be at an increased risk of developing intussusception because of dietary factors. For example there is evidence in animals as well as humans that diet may be an important factor in the pathogenesis of intussusception. When Cunnane and colleagues studied the Syrian Golden hamsters to determine the effect of diet on their fatty acid and lipid composition, intussusception was precipitated in 13% of the hamsters in the study within 7 to 10 days of changing diets from standard laboratory-grade rodent chow to a nutritionally complete semipurified diet high in sucrrose. Variations in dietary fatty acid composition had no effect, and the incidence of intussusception was reduced to zero on changing the carbohydrate source from sucrrose to maize starch. The investigators concluded that the "absence of intussusception in hamsters not fed on the sucrose-rich diet strongly suggests that bacterial or viral infestation in these hamsters was not sufficient alone to precipitate intussusception without the change in diet."

In humans, malnourished children are thought to be at lower risk of having an intussusception than well-nourished children. The risk of intussusception is believed to be related to the quantity of lymphoid tissue present in the ileocecal region in infants and young children. The lymphoid tissue of the GI tract is less prominent in very young and malnourished infants, therefore, these infants have less likelihood that enlarged mesenteric lymph nodes and Peyer's patches would result in the invagination of the terminal ileum into the cecum. Piscan et al. performed a case-control study of infants 12 months of age and younger to determine whether breastfeeding might have a protective effect on development of intussusception. This study found that participating infants who were exclusively breastfed had a sixfold increased risk, whereas partially breastfed children had a two- to threefold increased risk when compared with children who had never been fed with human milk. These data suggest that exclusive breastfeeding might be a risk factor for intussusception in infancy although no clear mechanisms by which this might occur is evident at this time. Additional analysis of the CDC's case-control and cohort study data may provide more insight into the relationship between intussusception and diet and nutritional status.

**KNOWLEDGE GAPS**

Data linking microorganisms, such as adenovirus and enterovirus, to intussusception are limited. Although earlier reports from Japan have suggested an association between natural rotavirus infection and intussusception, epidemiologic data presented at this workshop do not support such an association. Little is known about the pathogenesis and risk factors associated with idiopathic intussusception, which makes it difficult to determine why RRV-TV may be associated with this condition. The following fundamental gaps in knowledge were identified during the meeting.

**Specific Identifiable Factors (Agent and Host) That Increase Risk for Development of Intussusception Are Unknown**

**Diet and Feeding**

Children who develop intussusception generally have been described as "healthy, sturdy, well-developed, and well-nourished." The studies described above by Piscan et al. and Cunnane et al. provide data to support this concept, although quantitative assessments of nutritional status were not performed. Many protective factors (antibodies, glycoconjugates, cells, and antiinflammatory compounds) are present in human milk. In addition, bifidobacteria and lactobacillus are present in greater quantities in stool of breastfed infants when compared with stool of formula-fed infants. If the relationship between human milk and intussusception suggested by Piscan and colleagues is confirmed, the potential role of these factors will require additional evaluation.

**Age and Immune System**

Preliminary data from the multistate case-control study showed intussusception to be independent of age at which the first dose of RRV-TV was administered. Immunization with RRV-TV does induce an immune response that may protect against intussusception caused by RRV-TV. This might explain why the relative risk of intussusception after the second dose was less than after the first dose, regardless of age. Risk of intussusception after the third dose was negligible, although the number of children who received 3 doses was small.

**Gastrointestinal Tract Infection**

As mentioned previously, nearly all children develop rotavirus infection in the first 3 years of life with many experiencing multiple episodes. Most infants and young children also develop infections with other enteric viruses including astroviruses, enteric adenoviruses, and caliciviruses. Many of these infections are asymptomatic or not documented. The potential role of these organisms as a trigger or predisposing factor for the development of intussusception after RRV-TV administration is not known.

**Rotavirus NSP4**

Diarrhea is induced when the rotavirus nonstructural glycoprotein NSP4, acting as a viral enterotoxin, triggers a signal transduction pathway. NSP4 is an intracellular receptor that mediates the acquisition of a transient membrane envelope as subviral particles bud into the endoplasmic reticulum. Puri-
fied NSP4 or a peptide corresponding to NSP4 has been shown to induce diarrhea in mice. The diarrhea response was age-dependent, dose-dependent, specific, and could be blocked by drugs that affect Ca²⁺ transport. A mutation of a single amino acid ablated the effect; additional evaluation of NSP4 to clarify the molecular biology and clinical significance is ongoing. The association of NSP4 with intussusception is not known.

Other Oral Vaccines
Other orally administered vaccines such as oral polio vaccine have been administered widely in the United States. Available data could be analyzed to elucidate if association exists between other orally administered vaccines and intussusception.

Evidence for a Plausible Biological Mechanism Through Which RRV-TV–Associated Intussusception May Occur Is Limited
Lymphoid Hyperplasia
Although lymphoid hyperplasia is a nonspecific reactive change that may occur anywhere in the intestinal tract, it occurs more often within the distal portion of the ileum or rectum. Lymphoid tissue found throughout the submucosa of the small intestine commonly present as aggregates of lymphoid follicles known as Peyer’s patches. These Peyer’s patches increase in quantity in response to stimuli such as viral infection. Lymphoid response to a variety of stimuli is most active during childhood; adenoviruses and enteroviruses have been documented as examples of such stimuli.29

Intestinal Motility
In the mouse, intussusception spontaneously reduces, and there is anecdotal evidence to suggest that intussusception in humans also frequently self-repairs. A better understanding of the conditions under which self-repair occurs would be helpful in determining the potential role of specific vaccine antigens.

Inoculum Size
The dose of RRV-TV administered to infants is higher than the inoculum of wild-type rotavirus that is ingested. This large inoculum may in some way trigger development of intussusception in a susceptible host.

Characteristic of RRV-TV
RRV-TV was developed with the goal of combining the specificity of the epidemiologically important G serotypes with the attenuation phenotype of RRV. Reassorted strains were selected as vaccine strains because their VP7 gene representing serotypes G1, G2, and G4 was derived from their human rotavirus parents, but the remaining 10 genes were derived from RRV. Perhaps one of the gene products from the RRV is associated with intussusception in a susceptible host.

Understanding the mechanisms by which intussusception occurs has implications for whether RRV-TV could be administered according to an alternative schedule to avoid this complication. For example, if hypertrophied Peyer’s patches do have a role in development of intussusception, earlier administration of the first dose of RRV-TV might reduce the risk. Because Peyer’s patches take several months postnatally to mature there might be a lower risk of natural intussusception during the first few weeks of life. A number of proposed studies in developing countries, now on hold as a result of identification of this adverse event, were designed to administer RRV-TV at birth.

RESEARCH PRIORITIES
If discrete host or environmental factors exist for intussusception, it is conceivable that RRV-TV served as a trigger in children otherwise predisposed to develop intussusception. Numerous factors (microbiologic, environmental, behavioral, genetic, and vaccine characteristics) need to be considered and evaluated for their possible roles in the association between RRV-TV and intussusception. Future studies should address the fundamental knowledge gaps identified during the meeting.

Pathophysiologic Studies
1. Use existing animal model(s) to evaluate the following:
   a. Whether oral ingestion or immunization with homologous or heterologous host rotaviruses or with candidate rotavirus vaccines result in lymphoid hyperplasia/hypertrophy in gut-associated lymphoid tissues, and/or motility changes, including a determination of how these effects vary with age and inoculum size; and
   b. Whether host nutritional status and/or genetics play a role in the development of intussusception.
2. Improve existing animal models, and develop new models and novel approaches.

Epidemiologic and Clinical Studies
1. Prospectively study children with intussusception with a focus on epidemiology, genetic factors, clinical presentation, intestinal microbiology, and pathology.
   a. Risk factors for idiopathic intussusception need to be defined; these data may lead to a strategy for minimizing the risk of intussusception possibly associated with the use of RRV-TV, such as changing the dose of RRV-TV, the dosing regimen, or the age of administration.
   b. The role of genetic factors that may predispose the host to intussusception after RRV-TV administration should be elucidated.
2. Define the baseline incidence of intussusception, especially in developing countries. This information will enable a more precise consideration of vaccine risks and benefits for children living in countries where morbidity and mortality potential from rotavirus infection is higher than in the United States.
3. Define the overall attributable risk of intussusception associated with RRV-TV.
4. Continue to gather data about the burden of rotavirus disease.
5. Clarify the specific pathology involved in intussusception.

Benefit-Risk Considerations

The benefit-risk considerations for use of a rotavirus vaccine in the United States are quite different from those in developing countries. Although rotavirus infection in the United States results in substantial hospitalizations, but little mortality, rotavirus infection in the developing world is a major cause of mortality. The balance of risk and benefit for rotavirus vaccines depends heavily on the setting, and greatly influences decisions about the use of RRV-TV as well as new rotavirus vaccines.

Vaccines are given to healthy children and are, therefore, held to a higher standard of safety than other medical interventions. In contrast to adverse events, benefits achieved from vaccines are not immediately perceived, particularly on an individual level. Assessments of risks and benefits have to be made in terms of morbidity and mortality prevented, productivity losses avoided, and diagnosis and treatment costs saved. Even when a favorable benefit-risk relationship exists on a societal level, a highly visible and potentially serious risk like intussusception can make a vaccine unacceptable for routine use unless the disease it prevents is severe, and public demand for the vaccine is substantial. Future rotavirus vaccine studies will need to be performed in settings where intussusception can be rapidly recognized and effectively treated.

CONCLUSION

Determining the cause of and the pathophysiological basis for idiopathic intussusception, as well as its association with the RRV-TV vaccine, will require extensive research, including the generation of sound epidemiologic data from the United States and developing areas of the world. Improved surveillance for rotavirus infection and intussusception will be particularly important for developing countries if RRV-TV and other rotavirus vaccines are to be evaluated for safety and efficacy, and ultimately used in those areas.

Several candidate rotavirus vaccines, including another reassortant vaccine (WC3 bovine human reassortant) are being explored. Although it will be several years before another rotavirus vaccine is available, international collaboration will be needed to develop studies that will provide the required data for the formulation of appropriate policies for the future administration of rotavirus vaccines worldwide. It is important to note that the benefit/risk and ethical considerations are as crucial as the science if optimal public health is to be assured. In addition, lessons learned from the study of intussusception and RRV-TV can be applied to, and may influence the development of other oral vaccines.

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7 of 7

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