Intussusception, Rotavirus, and Oral Vaccines: Summary of a Workshop

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ABSTRACT. Rotavirus gastroenteritis continues to cause substantial morbidity and mortality worldwide, despite widespread breastfeeding and use of oral rehydration therapy. This burden of disease indicates that an effective, safe rotavirus vaccine is needed, and in 1998 the first rhesus-human reassortant rotavirus tetravalent vaccine, Rotashield, was licensed in the United States. However, the recommendations for its use were withdrawn in 1999 because of the recognition of an uncommon but serious adverse event, intussusception. A workshop in September 2001 was held to review the subsequent developments and research regarding this association, the proceedings of which are summarized here. Although the pathogenesis of this association remains unknown, epidemiologic evidence supports a causal relationship, with a population attributable risk of ~1 per 10 000 (range of 1 in 5000 to 1 in 12 000) vaccine recipients. Whether this association will exist with other candidate rotavirus vaccine strains and whether the attributable risk for intussusception would be similar in other populations administered this vaccine are unclear. Because perceptions of vaccine safety derive from the relative disease burdens of the illness prevented and adverse events induced, the acceptance of rare adverse events may vary substantially in different settings. Nevertheless, a continuing consensus on the need for a safe and effective vaccine to prevent rotavirus gastroenteritis, especially for use in developing countries, exists. *Pediatrics* 2002;110(6). URL: http://www.pediatrics.org/cgi/content/full/110/6/e67; *intussusception, oral vaccines, rotavirus, rotavirus infection, rotavirus vaccines.*

ABBREVIATIONS. CDC, Centers for Disease Control and Prevention; ACIP, Advisory Committee on Immunization Practices; RRV-TV, rhesus-human reassortant rotavirus tetravalent vaccine; NIH, National Institutes of Health; NVPO, National Vaccine Program Office; NVAC, National Vaccine Advisory Committee; WHO, World Health Organization; GAVI, Global Alliance on Vaccines and Immunization; NIAID, National Institute of Allergy and Infectious Diseases; VAERS, Vaccine Adverse Events Reporting System.

Because of the association of vaccination with intussusception, the Centers for Disease Control and Prevention (CDC) in the fall of 1999 on the advice of the Advisory Committee on Immunization Practices (ACIP) withdrew its recommendations for the use of the first licensed rotavirus vaccine in the United States. This product, Rotashield, is a live, orally administered rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) manufactured by Wyeth Laboratories (Marietta, PA). An initial workshop was convened by the National Institutes of Health (NIH) and the National Vaccine Program Office (NVPO) in January 2000 to focus research on understanding this possible association. The workshop identified critical areas of research regarding the association between RRV-TV and intussusception, which "will be essential not only for the development of safe and effective rotavirus vaccines but also for other oral vaccines."[1]

On September 5–7, 2001, a second workshop was held in Arlington, Virginia, by the National Vaccine Advisory Committee (NVAC) and the NVPO to review this research. The objectives of the 2001 workshop were as follows:

1. To provide a forum to examine data obtained since the January 2000 workshop.
2. To identify the burdens of intussusception and rotavirus infection in different populations.
3. To review recent information on the pathogenesis of intussusception.
4. To define the rate of intussusception after receipt of RRV-TV and other vaccines administered by the oral route.
5. To consider a means to compare the risks and benefits of candidate rotavirus vaccines.

The responsibilities of the NVAC are to advise the Department of Health and Human Services on programmatic policies concerning immunizations, whereas the ACIP makes technical recommendations on the use of vaccines. Major issues for the NVAC include enhancement of new and improved vaccines by fostering public and private sector collaborations, coordination of the multiple agencies in the federal government involved with prevention of disease through use of safe and effective vaccines, and enhanced related research. Thus, although this workshop focused on rotavirus vaccine, the discussions have broad implications for vaccine policy, such as the question of an acceptable risk for any given vaccine and management of these risks. In addition, the deliberations of this workshop were intended to serve as the basis for a subsequent review by the ACIP of recommendations pertaining to the use of RRV-TV, new rotavirus vaccines that may be considered for licensure, and other oral vaccines intended for use nationally and internationally.

In addition to the findings of the 2000 NIH/NVPO

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workshop, the discussions from 2 other related meetings held shortly thereafter were reviewed, one by the World Health Organization (WHO) and the other by the Global Alliance on Vaccines and Immunizations (GAVI). Among the conclusions of the WHO workshop was that the experience with RRV-TV should not discourage additional studies of rotavirus vaccines.[2] The consensus was clear that an urgent need exists for these studies, and failure to conduct them would be unethical. Considerable interest also was expressed in the possibility of initiating rotavirus immunization in the neonatal period, an option that has been only preliminarily investigated to date. The GAVI Task Force on Research and Development identified rotavirus vaccine as 1 of the top 3 priority vaccines for international development (unpublished data). This conclusion was similar to that made by a 1986 Institute of Medicine committee that identified rotavirus vaccine as a priority for developing countries where morbidity and mortality are greater than in the United States and other developed nations.[3] The GAVI Task Force had several specific proposals for assessing the risk of intussusception in association with rotavirus vaccination, including the need for methods to estimate risk, protocols for monitoring this risk, and a standard case definition. Of note, China is the only country that has a rotavirus vaccine in use, a lamb-derived strain. Very limited data are available about its efficacy and safety, including no information on the occurrence of intussusception in association with its administration.

DISEASE BURDEN

Dr Roger Glass of the CDC reviewed the considerable data accumulated before licensure of RRV-TV that demonstrated the significant burden of rotavirus gastroenteritis in the United States. These findings were summarized in the published recommendations by the ACIP and the American Academy of Pediatrics for routine infant immunization against rotavirus disease.[4,5] Dr Glass also noted 3 cost-benefit analyses of rotavirus vaccine, one of which is yet to be published, demonstrating that most of the costs of disease relate to hospitalizations.[6,7]

The reported incidence of hospitalization worldwide for rotavirus disease ranges from 1 in 16 children in Venezuela to 1 in 77 children in the United States. The current global burden of rotavirus disease is substantial, accounting for an estimated 452 000 deaths each year. This number is ~50% lower than that of the 1986 Institute of Medicine assessment, a decline that presumably is attributable to the increasing utilization of oral rehydration therapy worldwide. Nevertheless, rotavirus disease remains a leading global cause of infant and childhood illness and death, necessitating its prevention through vaccination.

VACCINE DEVELOPMENT

Dr Albert Z. Kapikian of the National Institute of Allergy and Infectious Diseases (NIAID), a leader in the efforts to develop a safe and effective rotavirus vaccine, provided a comprehensive review of past and current work on candidate rotavirus vaccines that spans the past 20 years. These candidate vaccines include monovalent, multivalent, and multiple reassortant vaccines. The immunogenicity, efficacy, safety, and characterization of the one US-licensed vaccine, RRV-TV, have been summarized in numerous publications, including the 1999 recommendations of the ACIP and the American Academy of Pediatrics.[4,5] Several of the noteworthy points by Dr Kapikian include the following:

1. A sentinel study that provided support for current rotavirus vaccination in a multiple dose strategy was performed in Mexico.[8] The findings demonstrated that children 0 to 24 months old experienced multiple wild-type rotavirus infections and protection against moderate to severe diarrhea results after 2 infections.
2. Immunity against rotavirus infection is serotype-specific, but both homotypic and heterotypic protection have been demonstrated. The extent to which a given serotype can generate heterotypic as well as homotypic protection is not resolved, but an effective vaccine will necessitate induction of protection against the 4 major rotavirus serotypes.
3. A pilot study of RRV-TV in Finland of ~90 infants divided into 3 groups, each of whom received a different vaccination schedule, demonstrated comparable immunogenicity by neutralization of RRV[8] and lack of fever at 2 months of age in a vaccine schedule initiated at birth and continued at 2 and 4 months of age in comparison to a schedule where the first dose was given at 2 months of age.[9] This finding potentially is very important for future vaccine strategies, especially in developing countries that use the immunization schedule of the WHO Expanded Program on Immunization, which is initiated at birth.
4. Multiple other rotavirus vaccine candidates evaluated in efficacy field trials include a quadrivalent bovine rotavirus-human rotavirus reassortant vaccine developed at the Wistar Institute (Philadelphia, PA) (currently in field trials by Merck Research Laboratories, Blue Bell, PA), a monovalent human rotavirus vaccine developed in Cincinnati (currently in field trials by Glaxo SmithKline, Philadelphia, PA), a quadrivalent bovine rotavirus developed in the United Kingdom, and a bovine-human rotavirus reassortant vaccine developed by NIH investigators and under testing by Wyeth Laboratories (Marietta, PA).

The data reviewed by Dr Kapikian were encouraging but demonstrated the challenges in developing a safe and effective rotavirus vaccine.

A prominent feature that emerged during the discussion that followed was the very different characteristics of the various candidate vaccines. Strains differ considerably in their ability to replicate in the human intestine. For example, whereas rhesus-human rotavirus vaccine strains have the capacity to replicate in the human small intestine and cause diarrhea in several species other than monkeys, bovine-human rotavirus vaccine replicates poorly in

human intestines requiring administration of a higher dose. In addition, the rhesus vaccine strains cause hepatitis in certain strains of inbred immunodeficient mice. They also have the capacity to replicate in vitro in the absence of trypsin. The degree to which these biological differences are important in the pathogenesis of intussusception in human infants and in immunogenicity remains unclear. A tantalizing unpublished finding presented by Dr John D. Patton of the NIAID was the hypervariability in gene 5 in the RRV-TV, which might be a significant clue in understanding the difference between this and other vaccine strains in their potential to induce intussusception.

INTUSSUSCEPTION RECOGNITION AND DISEASE BURDEN

Although considerable data on the relationship of RRV-TV and intussusception has been obtained since the first workshop, the continuing lack of knowledge of the etiology, epidemiology, and pathophysiology of intussusception was clear. Several investigations involving imaging studies in small numbers of young children with wild-type rotavirus gastroenteritis, however, have demonstrated abdominal nodal enlargement and increased bowel wall thickening but not increased peristalsis. Whether these changes are specific to rotavirus infection has not been determined.

Dr Julie Bines from Melbourne, Australia, summarized a WHO review of 269 published studies of intussusception from 70 countries. The incidence of intussusception varies in different countries. In most developed countries, the incidence of intussusception in the first year of life is <1 per 1000. The incidence in the United States appears to be lower than that in other countries, such as Japan, and the incidence fluctuates yearly. Although the incidence in developing countries appears to be lower than that in industrialized areas, the extent to which this difference relates to decreased detection and differing case definitions is not clear. Furthermore, the incidence of intussusception appears to be increasing in some countries, such as China, Ghana and the West Indies, and decreasing in others, such as Scotland, Nigeria and possibly the United States. Dr Bines also noted that the triad of rectal bleeding, vomiting and abdominal pain, classically associated with intussusception, has been reported to range from 10% to 82% in different studies. Another finding was that the mortality in developed countries of 0.3% is much lower than that in developing countries where it can be as high as 54%. Of particular note, this WHO assessment resulted in a clinical case definition, which has been validated in a study in Melbourne, Australia, with a sensitivity of 96% and specificity of 99%. On publication, this case definition should be very helpful in future surveillance of intussusception in vaccine trials and postlicensure studies.

In a study in progress, Dr Robert Chen and his colleagues at the CDC, in a continuing review of the RRV-TV-related events reported to the Vaccine Adverse Events Reporting System (VAERS), identified reports of blood in stool, including rectal bleeding, currant jelly stools, and/or blood in rectal mucous. Of the 37 VAERS reports, 10 were categorized as serious and 27 as nonserious. The distinguishing features in this categorization were whether an infant was hospitalized, was disabled, suffered a life-threatening illness, or had a prolonged hospital stay. These stool and rectal findings occurred 3 to 7 days after vaccination and were not reported in association with administration of other vaccines. Whether these cases represent a prodrome of intussusception or a reporting bias remains to be determined but will need to be considered in the design of future rotavirus vaccine trials.

Dr Mary Allen Staat of Children's Hospital Medical Center of Cincinnati reviewed the little data available that examined the epidemiology and disease burden of intussusception in the United States and reported on her recent study, which defined the rate of intussusception for the population of Hamilton County, Ohio, from 1990 through 2000.[10] This study illustrated the shortcomings of using hospital data to assess the risk of intussusception. She noted the following 3 pitfalls: inaccurate identification of patient residence, incorrect coding of diagnoses, and variable management of intussusception. For example, as many as 40% of children with intussusception remain in the hospital for <24 hours, and these short-stay admissions are not considered hospitalizations. She also reported that the proportion of cases that are hospitalized varies from year to year.

In a study from New Delhi, no cases of hospitalized patients with intussusception in an encatchment area of 48 000 infants were detected, suggesting that either intussusception may be less common in developing countries or children with intussusception are not brought to a hospital. However, this study, currently in progress, was able to detect 12 intussusception cases outside of the encatchment area.

INTUSSUSCEPTION PATHOGENESIS

The pathogenesis of RRV-TV-associated intussusception in humans remains an enigma. A CDC study of pathologic specimens from cases of intussusception associated with RRV-TV has used highly sophisticated molecular biological techniques, but the number of specimens available to the investigators was limited. No significant clues to the pathogenesis of intussusception were found.

Dr Margaret E. Connor of the Baylor College of Medicine reviewed the results of their investigations using an experimental murine model of intussusception induced by lipopolysaccharide. Murine rotavirus strains enhanced the rate of intussusception in this model, causing enlargement of mesenteric lymph nodes and Peyer's patches. However, Peyer's patches did not appear to be the anatomic lead point for intussusception. The investigators further demonstrated differences in the ability of rotavirus strains to increase the murine incidence of intussusception. For example, the bovine rotavirus strain WC-3 and inactivated rhesus rotavirus vaccine had no effect, but a simian strain did augment the occurrence of intussusception. Dr Connor and colleagues concluded that some strains of rotavirus could be a

cofactor in the induction of acute intussusception in mice. They were not able to demonstrate obstructive intussusception. Additional evidence of the variation in responses in mice to different strains of rotavirus was provided in studies performed by Dr H. Fred Clark and colleagues at the University of Pennsylvania School of Medicine.[11] Virus was detected in mesenteric lymph nodes and Peyer's patches after inoculation of simian-human but not bovine-human reassortants. The implications of these findings for humans, however, are unclear.

To date, studies have not demonstrated that wild-type rotavirus infection is associated with intussusception with the exception of case reports from Japan in the late 1970s.[12] Dr Nakagomi postulated that some strains, such as a G3 serotype, could induce intussusception whereas others may not. This finding might explain the yearly variation in the incidence of intussusception.

In a roundtable discussion of the relationship between RRV-TV and intussusception, Dr Paul Offit of Children's Hospital of Philadelphia offered 3 possible hypotheses. One is the "unique strain hypothesis," according to which the induction of intussusception is related to the rhesus rotavirus vaccine strains but not to other vaccines or wild-type strains. The second is that of a "bolus dose," in which ingestion of an inoculum of high viral titer by an infant is necessary to induce this disorder. A third is the "viral replication" hypothesis in which wild-type rotaviruses are a rare but consistent cause of the disease.

ROTASHIELD ASSOCIATION WITH INTUSSUSCEPTION

Prelicensure studies demonstrated that RRV-TV prevents severe rotavirus disease and causes only mild adverse events, specifically low-grade fever and irritability.[4,5] Five cases of intussusception occurred but were consistent with the background rate of this disorder. Nevertheless, this occurrence alerted the public health community to the need for postlicensure surveillance. The resulting scrutiny led to the early recognition of a cluster of cases and an increased incidence of intussusception in temporal association with administration of RRV-TV, particularly the first dose. Approximately 1 million doses were estimated to have been administered according to CDC surveillance and information provided by Wyeth Laboratories.

The 6 studies evaluating the temporal association of RRV-TV with intussusception were reviewed in detail.[13–17] They differed in methodology: 2 were ecological,[14,15] 1 was a case-control,[13] another was a case-series,[13] and the others were retrospective cohort studies.[14,17]

Murphy et al[13] in a case-control and case-series studied hospitalized patients with intussusception in 19 states and found a significantly increased risk of intussusception 3 to 14 days after the first dose of RRV-TV. The risk was most marked in the 3- to 7-day period. The risk also was increased after the second dose, although to a lesser extent. These investigators noted an attributable risk of intussusception after vaccination of 1 case for every 4670 to 9474 vaccinated infants. Three weeks after vaccination in the case-control study, the risk was <1. Dr Murphy noted that this lowered odds ratio reflected a return to the baseline incidence rate and that infants with markers of higher socioeconomic status were more likely to have received RRV-TV and to have a lower baseline risk of an intussusception than those infants who did not receive the vaccine. They concluded that their data did not support a hypothesis of a compensatory decrease of intussusception after vaccination. According to their findings, the total number of cases of intussusception would have been increased by 28% if a national program of rotavirus vaccination had been fully implemented.

In a retrospective cohort study involving 10 large managed care organizations, Kramarz et al[14] also demonstrated an increased risk of intussusception in the 3- to 7-day period after the first vaccine dose. Of the 67 cases initially identified in the computerized database of diagnoses, only 60% were confirmed by medical chart review. The attributable risk in this study was 1 case of intussusception per 11 073 vaccinated infants. The CDC Vaccine Safety Datalink Group reported preliminary results of their ongoing study of this initial investigation by Kramarz and colleagues in which infants are followed until 1 year of age. The increased risk of intussusception 3 to 7 days after vaccination again was demonstrated. The relative risk after 21 days was ~1 and did not suggest a compensatory decrease. The results were based on small numbers, however, and are not definitive.

Chang et al[15] in an ecological study of hospital discharge data from 1989 through 1998 in New York reported data suggesting that the rate of intussusception had declined during this period. The rate of intussusception was ~1 in 2600 infants. Their findings did not demonstrate an appreciable increase in the incidence of intussusception after the introduction of rotavirus vaccine, leading to the question of whether the rate of intussusception after vaccination was lower than the original CDC estimate of 1 in 2500 to 5000 recipients of RRV-TV.

Simonsen and colleagues[16] at the NIAID reported the results of a 10-state and a subsequent 20-state ecological study of hospital admissions for intussusception. In the 10-state study, admissions among infants increased by an estimated 1% during the time interval of RRV-TV use. Their findings also demonstrated a decrease in intussusception hospitalizations from 1993 to 1999 and by trend comparison the increase during the time of RRV-TV use was 4%. Based on estimated vaccine coverage of 28%, the population attributable risk was 1 excessive hospital admission in 66 000 to 302 000 vaccine recipients of the first dose at 45 to 210 days of age. In their subsequent 20-state study, the findings were similar but the population attributable risk of 1 in 13 500 to 31 500 infants was higher. They based their estimates on the coverage rate determined in the National Immunization Survey, which was substantially less than that initially estimated. Thus, the intussusception risk in these ecological studies was substantially lower than that of previous estimates by CDC investigators and

might suggest that the increased incidence of intussusception after vaccination was accompanied by a compensatory decrease, ie, a temporal shift, which could be explained by a triggering mechanism of RRV-TV in the causation of intussusception.

In a capture-recapture study, Verstraeten et al[17] assessed the completeness of reporting to the VAERS in the case control and retrospective cohort studies by Murphy et al[13] and Kramarz et al[14] to be 47%. Their findings also demonstrated the increased relative risk of intussusception in the 3- to 7-day and 8- to 14-day periods after vaccination.

After the presentations of these studies, the conclusions of an expert panel[a] were as follows:

1. The evidence clearly indicates a causal association of RRV-TV and intussusception. This association, as demonstrated in the CDC case-control and case-series studies, was strong, temporal, and specific.
2. The ecological studies demonstrated that an epidemic of intussusception did not follow the introduction of rotavirus vaccination. However, vaccine coverage was only 12.8%, according to National Immunization Survey data. Coverage varied from a low of 0 in New Mexico to a high of 27% in Wisconsin.
3. Although the studies differed in methodology, strengths and limitations, the consensus was that the population attributable risk of intussusception was ~1 per 10 000 children administered RRV-TV, ranging from a high of 1 in 5000 to a low of 1 in 12 000. These estimates contrast with the initial estimates of 1 in 2500 to 5000.
4. The question whether the rhesus rotavirus vaccine was a trigger for an event predestined to occur, ie, intussusception, was debated at length. The 3 ecological studies, 2 by NIH investigators and the other in New York state, did not demonstrate a significant increase in intussusception rates during the 1998–1999 period of RRV-TV usage. If so, the NIH investigators postulated that the increased incidence of intussusception after the first dose of RRV-TV was associated with a compensatory decrease after the first 3 weeks' postvaccination, ie, a temporal shift. However, the limitations of the ecological studies led to the conclusion that this hypothesis, although intriguing, was not proven.

INTUSSCEPTION AND OTHER ORAL VACCINES

A possible association of intussusception with administration of other oral vaccines, specifically the oral polio vaccine, has been investigated. Studies in the United States, the United Kingdom, and Cuba did not confirm an association. Although several studies suggested a possible association, the findings were inconsistent and the majority of experts convened at the CDC in June 2000 concluded that the data were sufficient to reject a causal relationship between oral polio vaccine and intussusception. Some, however, did not believe that the data were sufficient to exclude such a relationship.

ASSESSMENT AND IMPLICATIONS OF RISK AND BENEFIT

The complexities of the critical issues of vaccine policy in assessing and managing risk and benefit were emphasized by the different perspectives provided by the following: Dr David M. Salisbury, Principal Medical Officer of the United Kingdom Department of Health; 2 pediatricians from the United States, Drs Edgar K. Marcuse of the University of Washington and Thomas N. Saari of the University of Wisconsin; Dr T. Jacob John, an advisor to the Kerala State Institute of Virology and Infectious Diseases in India; and Dr Charles Weijer, a bioethicist from Dalhousie University in Nova Scotia. Dr Salisbury noted that perception of risk by the public is as important as the demonstrated risk as illustrated by several examples in recent years in the United Kingdom, such as with measles-mumps-rubella vaccine and autism. Although perceptions of risks are not necessarily substantiated, they can be very influential. This perception also is influenced by opinions of health professionals and the media, both of whom are important elements in forming public opinion. Communication of risk, therefore, is a major challenge. Dr Salisbury reviewed the program of risk perceptions and communications by the United Kingdom Department. He asked the critical question of what risk of intussusception from RRV-TV would the United States have tolerated or accepted to continue vaccination.

In the subsequent discussion of critical issues in vaccine policy, Dr Marcuse distinguished risk assessment from risk management. Thus, in assessing risk and benefit, technical, philosophical and procedural perspectives may lead to differing policy options. For immunization, these options include the following: not recommending the use of a vaccine; elective vaccine usage; selective recommendations for vaccine targeted to high-risk groups; universal immunization; and mandated use of vaccine. To be effective, risk management requires consensus building among public health workers, the medical community and the public, including the support of both appointed and elected officials in government.

Dr Saari reviewed the results of a survey he performed of pediatricians and family physicians in Wisconsin on rotavirus vaccine utilization and opinions. The findings demonstrated that from the private practice perspective, the risk of an adverse event in recommending a vaccine needs to be considered in the context of the severity of the adverse event. Physicians have a community, not a national, frame of reference that is based on their practice experiences, vaccine costs, and anxiety in parents. This anxiety might generate increased phone calls and medical visits, resulting in unanticipated and increased use of medical resources. A key problem is that a rare adverse event after immunization necessitates availability of specialty care, such as experienced radiol-

[a]Drs John LaMontagne of the NIAID, Walter A. Orenstein of the CDC, James J. Schlesselman of the University of Miami School of Medicine, Eugene D. Shapiro of the Yale University School of Medicine, and Alexander M. Walker of the Harvard School of Public Health.

ogists and pediatric surgeons in the case of intussusception, which may not be readily available in rural or underserved communities. In contrast to febrile convulsions, intussusception is an event not common in the daily practice of physicians caring for children.

THE FUTURE

The workshop concluded with a review of developments with implications for the future prevention of rotavirus infections. Representatives from Merck Research Laboratories and Glaxo SmithKline described the status of their ongoing trials of 2 candidate rotavirus vaccines, a pentavalent simian-human reassortant and a human-derived strain isolated in Cincinnati, respectively. Other interventions than vaccination for limiting the morbidity and mortality of rotavirus infection, reviewed by Dr Larry Pickering of the CDC, are oral rehydration therapy and breastfeeding. Dr Pickering noted the relatively low utilization of oral rehydration therapy in the United States and the protective factors in human milk against gastroenteritis.

CONCLUSION

The 3-day meeting was marked by a lively, spirited discussion and comprehensive review of the considerable new information elicited by investigators since RRV-TV vaccination was suspended in 1999. The purpose was to provide the information necessary to guide future public health policy for the prevention of rotavirus gastroenteritis. The federal and other vaccine advisory committees will need to consider this information in their roles of providing guidance in the development of national vaccine policy. The meeting also demonstrated that although considerable progress has been made in understanding the association of intussusception and RRV-TV, major unanswered questions remain. Nevertheless, at least 3 clinical studies to assess new candidate rotavirus vaccines are in progress. Although an effective rotavirus vaccine remains a priority for the United States, the major challenge is how the United States and the world health community can foster and expedite the development of rotavirus vaccines for use in the developing world where the morbidity and mortality of this disease greatly exceeds that in the United States.

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