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The First Rotavirus Vaccine and the Politics of Acceptable Risk

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Context: Vaccination in the United States is a frequent source of controversy, with critics alleging failures by public health officials to adequately identify, monitor, and respond to risks associated with vaccines. In response to these charges, the case of RotaShield, a vaccine withdrawn in 1999 following confirmation of a serious adverse event associated with its use, is regularly invoked as evidence of the effectiveness of current vaccine safety activities.

Methods: This article examines the history of RotaShield, with particular attention paid to decision making regarding its use in the United States and internationally. I reviewed and analyzed federal advisory committee meeting transcripts, international conference reports, government and scientific publications, media coverage, and other primary and secondary source materials. I also conducted six semistructured interviews with former senior officials and advisory committee members at the U.S. Centers for Disease Control and Prevention who participated in decisions regarding the vaccine.

Findings: Decision making regarding RotaShield, including the ultimate withdrawal of its recommendation for use, was shaped significantly by government health officials' concern for preserving public confidence in overall U.S. vaccination efforts amid several unrelated vaccine risk controversies ongoing at that time. This attention to public perception and external pressures occurred in tandem with the evaluation of the quantitative evidence regarding the magnitude and severity of the risk associated with the vaccine. The decisions made in the United States resulted in foreseen but unintended consequences for

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international use of the vaccine, including in nations where the profile of risks and potential benefits was dramatically different.

Conclusions: As enthusiasm for evidence-based decision making grows throughout medicine and public health, greater explicit attention should be directed to the processes by which decision makers and their expert advisers evaluate such evidence and translate it into regulation and policy by means of qualitative judgments.

Keywords: Rotavirus vaccines, intussusception, safety, risk, vaccination, policymaking.

On October 12, 2010, the U.S. Supreme Court heard oral arguments in the case of *Bruesewitz v. Wyeth LLC*. The question before the court was whether a 1986 federal law that created a compensation program for individuals injured by vaccines also barred most civil claims against vaccine manufacturers under state laws. Even among the numerous recent controversies regarding the safety and necessity of vaccines, this case was viewed by public health officials as particularly important to the continued success, if not the viability, of the U.S. vaccination landscape that the 1986 law was intended to protect (Evans, Levine, and Jacobs 2012).

The United States filed an *amicus curiae* brief in the case supporting the position of the respondent, Wyeth LLC (Brief 2010). In its brief, the government noted the importance of the law as part of its efforts to ensure the continued availability of vaccines, to monitor their safety, and to compensate individuals harmed by them. To illustrate the effectiveness of vaccine safety surveillance mechanisms, the brief described the case of RotaShield, a vaccine against severe diarrheal disease that was removed from the market in 1999 following the identification of a rare but serious adverse event associated with it. The government wrote:

> Events surrounding the withdrawal of the Rotashield vaccine illustrate how well this system functions in practice. . . . In the space of about one year, a vaccine was licensed and recommended for routine administration, adverse events raised a concern, further studies were conducted, and the manufacturer withdrew the vaccine knowing the government and physician community were ready to respond. (Brief 2010, 23–24)

The Supreme Court's February 2011 opinion in favor of Wyeth—thereby limiting civil claims against vaccine manufacturers—was viewed as a victory by advocates of vaccination, including the American Academy of Pediatrics and twenty-one other medical organizations that had jointly filed an *amicus curiae* brief supporting Wyeth's position (American Academy of Pediatrics 2010; *Bruesewitz v. Wyeth* 2011; McAbee, McDonnell, and Donn 2011). Nevertheless, vaccination in the United States remains a frequent source of controversy, with critics alleging failures by public health officials to adequately identify, monitor, and respond to risks associated with vaccines (Kirby 2005; National Vaccine Information Center 2012).

In response to these charges, the RotaShield story is regularly invoked as evidence of the effectiveness of vaccine safety activities in the United States. Synopses similar in approach and scope to the account in the Supreme Court *amicus* brief can be found throughout the medical literature, in congressional testimony, and in public health planning documents (e.g., Abramson and Pickering 2002; Griffin, Braun, and Bart 2009; Satcher 1999). In each of these tellings, the experience of RotaShield offers a clear, singular lesson: that the systems established to detect and respond to vaccine safety concerns are effective.

Limiting the legacy of RotaShield to little more than "the system worked, therefore the system works" ignores the broader insights and lessons that can be gleaned from a deeper examination of this brief chapter in the history of public health and vaccine policy. Transcripts of government advisory committee meetings, other published and unpublished materials, and interviews with former public health officials and advisers help illuminate the decisions made, the rationales for those decisions, and their consequences in the United States and internationally. Such an examination provides a previously unseen view of how public health officials and their expert advisers assess risk and benefit in the context of disease prevention policy.

The story of RotaShield highlights the value of the continued expansion of scholarship on risk and pharmaceutical prevention to include historical and sociological studies of decision making regarding interventions found to significantly *increase* some types of risk, particularly in the unique case of vaccines (Light 2010). Such efforts would complement recent work examining disease definitions and related products designed, developed, and marketed principally to *reduce* risk (Aronowitz 1998; Greene 2007).

The rise and fall of RotaShield demonstrates how social values and external considerations interact with empirical evidence throughout the decision-making process and in communications to the public. It also reveals how decisions by U.S. officials for domestic public health influence the fates of medical interventions globally, particularly for developing nations. As the implementation of a new generation of rotavirus vaccines expands in both the United States and worldwide, the lessons and consequences of the RotaShield experience continue to shape dialogues regarding vaccination programs and ongoing debates regarding the safety of vaccines.

Rotavirus and the Path to a Vaccine

Rotavirus infection is virtually universal among infants and young children and is the most common cause of severe diarrhea worldwide in this population (Clark et al. 2008). In the United States, rotavirus caused an estimated 2,700,000 symptomatic infections, 600,000 physician visits, and 55,000 to 70,000 hospitalizations annually before the introduction of second-generation vaccines in 2006 (Glass et al. 1996). Due to the availability of both oral and intravenous rehydration therapy in the United States, the number of deaths from this large number of infections and hospitalizations was limited to twenty to sixty deaths per year in the prevaccine era.

The worldwide profile of rotavirus-related morbidity and mortality, however, is dramatically different. Symptomatic infection is similarly widespread in young children globally, but because of the challenges in providing adequate rehydration to affected children, the virus is a far greater cause of death. An estimated 453,000 deaths are attributed to rotavirus-related illness worldwide each year, with the most severe impacts found in South Asia and sub-Saharan Africa (Tate et al. 2011a). The overwhelming majority of deaths in the United States and worldwide occur in young children three years of age or younger. Although the virus remains common throughout life, it is not a significant source of severe illness in older children or adults.

The development of vaccines against rotavirus had been a priority of the research community since the early 1970s, within a few years of the discovery of the virus itself (Marwick 1998). By the late 1980s, the leading vaccine candidate was a live simian-human reassortant virus developed at the U.S. National Institutes of Health (NIH) by Albert Kapikian and his colleagues. An investigational new drug (IND) application was initially filed in 1987, and early clinical testing of this vaccine, known as RRV-TV ("rhesus rotavirus—tetravalent") was favorable (FDA 1997). The NIH subsequently licensed the candidate vaccine to Wyeth Vaccines for large-scale clinical research and development and interaction with U.S. regulatory agencies.

Regulatory Review and Approval

Throughout the 1990s, before filing a product license application in 1997, Wyeth expanded clinical testing of the vaccine, which had then been given the brand name RotaShield (FDA 1997). Some of Wyeth's twenty-five clinical studies were carried out abroad, principally in South America and Europe. However, the manufacturer chose to pursue approval and introduction of the vaccine in the United States before taking parallel actions in other nations and regions, including those where the impact of rotavirus-related disease was greatest. Wyeth's hope was that the establishment of a large, profitable market for the vaccine in the United States would, in essence, subsidize later efforts to bring the vaccine to developing nations (CDC 1999c, 156).

Similar to pharmaceuticals and medical devices, vaccines require approval from the Food and Drug Administration (FDA) in order to be marketed in the United States. The agency's Center for Biologics Evaluation and Research receives guidance in this work from the Vaccines and Related Biological Products Advisory Committee (VRBPAC), a group of experts in vaccine science and related disciplines, as well as representatives from industry and consumer groups.

In December 1997, a nearly twenty-year period of basic and clinical research contributing to the development of RotaShield was concluding, and Wyeth presented the results of this research at a six-hour meeting of VRBPAC in Bethesda, Maryland. Results regarding the efficacy of the vaccine were highly favorable. At its final dosage, the vaccine was 49 to 68 percent efficacious against all rotavirus-related disease and 69 to 91 percent efficacious against severe diarrhea, the cases most likely to result in hospitalization or death (CDC 1999e). These levels of efficacy were comparable to those of most routinely administered vaccines in the United States. The vaccine's safety profile was similarly positive, limited primarily to minor concerns such as mild fevers observed in some vaccine recipients shortly after administration.

Midway through the day, Dr. Carolyn Hardegree, director of the Office of Vaccines Research and Review at the FDA, asked about cases of intussusception observed during clinical testing. Intussusception is an uncommon condition in which a portion of the intestine descends, or telescopes, into a distal segment (Hackam et al. 2010). Most common among infants in the first year of life, it can result in severe abdominal pain and a risk of intestinal blockage and compromised blood flow to the affected area. If diagnosed promptly, intussusception can often be resolved without surgery. But in severe cases not promptly diagnosed or treated, surgical resection of the affected portion of intestine may be required, and the condition can be fatal.

Dr. Margaret Rennels, a professor at the University of Maryland, led the multicenter clinical trial of RotaShield and was a lead presenter on behalf of Wyeth throughout the meeting. Responding to Dr. Hardegree's inquiry, she noted that five cases of intussusception had been found among the recipients of the vaccine, compared with none among the placebo groups. (A single case was later identified in the control group.) The cases occurred following the final two doses of the three-dose vaccination series, but the difference in the rates of intussusception between vaccinees and controls was not statistically significant, due to the size of the study populations.

"I was concerned that with larger numbers perhaps a causal relationship might emerge," Dr. Rennels told the committee (FDA 1997, 188). Asking for five minutes to elaborate on her follow-up work in response to this possibility, she was informed by the committee chair that only "a minute or two maximum" was available. In that time she summarized a literature review regarding estimates of the general frequency of intussusception (known as the "background rate") and concluded that "the intussusception was probably due to chance temporal association" (FDA 1997, 189).

There were no follow-up questions regarding Dr. Rennels's comments on intussusception and no further discussion regarding these data during the remainder of the meeting. The VRBPAC voted unanimously that RotaShield was safe and effective. Upon its licensure by the FDA on August 31, 1998, the following statement was included in the nineteen-page package insert: "Intussusception was noted in 5 of 10,054 (0.05%) vaccine recipients compared to 1 of 4,633 (0.02%) placebo recipients.

These rates of intussusception were not statistically significantly different and the rate observed among vaccinees was similar to that seen in comparison populations" (Wyeth-Ayerst 1998, 13). Identical text appeared in the small-print information included in advertisements for RotaShield published in pediatric journals beginning that fall, and a brief report published by Dr. Rennels and colleagues (1998) presented the same findings. Intussusception was not among the adverse reactions listed in an FDA press release issued upon the vaccine's licensure, nor was it among the specific focus areas for postmarketing studies that Wyeth was instructed by the FDA to conduct (FDA 1998a, 1998b).

Developing Recommendations at the Centers for Disease Control and Prevention

Vaccines are unique among medical interventions because of the equally important role of a second federal agency, the Centers for Disease Control and Prevention (CDC), in contributing to their success or failure. Whereas the FDA licenses vaccines for use in the United States, thereby approving them for marketing, the CDC issues recommendations regarding which populations should receive each licensed vaccine. It does so primarily through the work of its Advisory Committee on Immunization Practices (ACIP), a panel of external advisers that includes members with expertise similar to that of the members of VRBPAC, as well as others with backgrounds in pediatrics and public health practice (Smith 2010). A "recommendation" may imply only a modest statement of best practices for the medical and public health communities, but a broad CDC recommendation for a vaccine—an endorsement of its routine administration to all individuals at a certain age—is seen as essential to its medical and commercial success (Schwartz 2010).

While the review by the Food and Drug Administration was taking place, the CDC and the ACIP were developing draft recommendations regarding RotaShield. Their aim was to have guidance available to physicians as soon as possible following the vaccine's increasingly likely approval (CDC 1998a, 106). The vaccine had been discussed at every meeting of the ACIP for several years preceding its licensure. Information about RotaShield and intussusception was presented to the committee in June 1997, also by Dr. Rennels, and it was reviewed by its rotavirus working group in February 1998. The panel concluded then that the condition was not associated with vaccination, consistent with statements from senior CDC staff that "the safety of the vaccine is fairly well established" (CDC 1998a, 101, 104). The committee thus voted in favor of recommending routine immunization for all infants with three doses of RotaShield at ages two, four, and six months, pending continued deliberation at subsequent meetings. The discussions at those meetings focused on the cost-effectiveness of rotavirus vaccination programs and potential concerns related to minor fevers among the vaccine's recipients (CDC 1998b). Intussusception was not revisited.

The ACIP's recommendations become official upon approval by the CDC and publication in its *Morbidity and Mortality Weekly Report* (*MMWR*). For RotaShield, these recommendations were still being reviewed and amended at the February 1999 ACIP meeting (CDC 1999a), and they were not published until March 19, 1999, more than seven months after licensure (CDC 1999e).

Vaccination Begins and Concerns Emerge

By spring 1999, momentum for rotavirus vaccination had increased. The ACIP's recommendations had been published, followed by similar guidance from the American Academy of Pediatrics' Committee on Infectious Diseases (Jefferson 1999). RotaShield was a source of pride for its manufacturer, Wyeth, as well as a significant presence in the business plan of its corporate parent, American Home Products (AHP). In its 1998 annual report (released in early 1999), RotaShield is touted as one of AHP's "new, breakthrough therapies" (AHP 1999, 7). A feature in the report recounts a family's harrowing experience with severe cases of rotavirus-related disease. Below a family photo that includes two since-recovered, smiling girls is a quotation from their father: "No child should ever have to go through this. With RotaShield, they won't have to" (AHP 1999, 10–11).

As public awareness and enthusiasm for rotavirus vaccination grew throughout early 1999, so too did concern among CDC staff. By March 18, the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system jointly operated by the FDA and the CDC, had received sixty-two reports of adverse events potentially related to RotaShield (Wharton 2000). Created in 1990, VAERS allows anyone—patients, physicians, or third parties—to report adverse events that could be associated with a vaccine (Offit, Davis, and Gust 2008). The reporting is incomplete, requires follow-up investigation, and cannot directly distinguish temporal associations from causal associations. Consequently, VAERS functions as a hypothesis-generating mechanism, an early-warning signal of potential problems regarding vaccine safety.

Included among these initial sixty-two reports related to RotaShield were three cases of intussusception (Wharton 2000). Nine more reports of intussusception were submitted by June 17, when the next meeting of the ACIP was scheduled. Staff at the CDC had begun planning a rapid investigation of RotaShield and intussusception in order to determine whether the association suggested by the as-yet unconfirmed VAERS reports truly existed and, if so, its magnitude (CDC 1999b, 228).

Apologizing to the ACIP's members for the late addition of the session to their agenda, the CDC's Dr. John Livengood noted, "We felt that in the current climate, we shouldn't be seen as withholding information right now" (CDC 1999b, 206–7). As the session concluded, he commented on the CDC investigation occurring in a "nice, quiet media-neutral atmosphere," eliciting laughter from those in attendance (CDC 1999b, 236).

Livengood's comments hint at the particularly turbulent period facing the U.S. vaccination program and the government officials responsible for it. One year earlier, British physician Andrew Wakefield had published a paper in *The Lancet* suggesting an association between the measles-mumps-rubella (MMR) vaccine and autism spectrum disorder (Wakefield et al. 1998). The paper, since retracted by the journal and discredited, had a significant impact on vaccination rates in the United Kingdom, and the controversy received widespread attention in the United States (Harris 2010; Smith et al. 2008). Elsewhere during this period, the safety of thimerosal, a mercury-containing preservative used in many vaccines, was under scrutiny by groups including the CDC. Though subtle, Livengood's statements were the first acknowledgments of the context in which investigations and decision making regarding the safety of RotaShield were taking place.

The session at the June 1999 ACIP meeting was informational; its members made no recommendations and took no votes. Although the meeting had been open to the public and the media, there was no mention of intussusception in the media coverage of the vaccine before July 15, 1999 (Danavaro-Holliday, Wood, and LeBaron 2002). Since there had been no official statements to health care providers or parents regarding a possible safety problem with RotaShield, CDC staff drafted in late June a report for publication in *MMWR* (Wharton 2000).

Concerns over RotaShield first reached Dr. Jeffrey Koplan, the CDC director, on June 11 (CDC 1999c, 54). With multiple independent sources of information suggesting a possible risk associated with the vaccine, Dr. Koplan decided on July 13 to recommend that its use be temporarily suspended pending the completion of the ongoing investigations. Dr. Koplan viewed a temporary suspension as "buying time" for the CDC and ACIP until they had a clearer picture of the risks of the vaccine (Koplan 2009). Since rotavirus season typically came in late winter or early spring, delaying vaccination through the summer would have a minimal impact on protecting children against the disease (Orenstein 2009).

A report describing the cases of intussusception and announcing the recommended suspension was published in *MMWR* on July 16, 1999 (CDC 1999d). A front-page story in the *New York Times* that morning reported the decision while government health agencies and professional organizations hurried to spread the news to physicians. By that time, 1.8 million doses of the vaccine had been distributed since its licensure the previous summer, with an estimated 1.5 million doses then thought to have been already administered to 900,000 children (CDC 1999b, 215). The majority of vaccines administered in the United States are purchased by the federal government, but a contract for purchase of RotaShield had still not been reached because of protracted price negotiations with Wyeth. Recipients of the vaccine were therefore limited to those who obtained it via the private sector, in which the three-dose series was priced at $116 (Neergaard 1998; CDC 1999b). While RotaShield had been licensed in Europe in May 1999, it had not been distributed or used outside the United States (FDA 1999).

Concerns among ACIP members that the cases reported to VAERS represented "the tip of iceberg" were confirmed by the influx of additional reports of intussusception submitted in the initial weeks following the announcement of the suspension (CDC 1999b, 237). Eighty-three additional cases were reported to VAERS following the July 15 announcement, most within the first few weeks (Zanardi et al. 2001).

Work progressed through the summer of 1999 on the epidemiological studies designed to investigate the association between RotaShield and intussusception. It was a massive undertaking accomplished with remarkable speed, requiring the contributions of hundreds of CDC personnel and state and local public health officials. "We had a huge investigative team pulling people from all over the agency because of the support we had from the CDC director to get this done and get it done right," Dr. Walter Orenstein, the director of the CDC's National Immunization Program at the time, recalled (2009).

Several different study designs were employed, and the results of each suggested a substantial increased risk of intussusception among recipients of the vaccine, with the greatest risk occurring three to seven days after the first dose (T. Murphy et al. 2003). The strongest evidence of an association came from a case-control study that compared 429 infants hospitalized with intussusception between November 1, 1998, and June 30, 1999, with 1,763 matched controls. Researchers found statistically significant differences in RotaShield vaccination rates between the two groups (Murphy et al. 2001; Orenstein 2009). Based on these results and estimates of the background rate of intussusception among U.S. infants, the research team estimated one additional case of intussusception attributable to the vaccine for every 4,670 to 9,474 infants vaccinated (Murphy et al. 2001).

The End of RotaShield in the United States

The fate of RotaShield would be decided officially at the October 1999 meeting of the Advisory Committee on Immunization Practices, at which time the panel would revisit its recommendation in light of the newly obtained data regarding the safety of the vaccine. As the meeting date neared, it was evident to CDC staff and others aware of the results of the studies that there was no possible scenario in which vaccination with RotaShield would resume in the United States.

Although the CDC leadership virtually always accepts the recommendations of the ACIP, those recommendations emerge from a deliberative process in which CDC personnel are active contributors and partners throughout. "In all ACIP activities there is a very close relationship between the ACIP and the CDC technical staff who obviously participate and are involved in policy development at literally all stages and at all levels," observed Dr. John Modlin, the chair of the committee during this period (Modlin 2009). Recommendations are published in the name of the advisory committee, but they may be described more accurately as collaborative products developed by the committee and the CDC staff and approved by both entities. "When the ACIP makes a recommendation, CDC reviews it, and if it accepts it, it publishes it in the *MMWR*," Walter Orenstein explained (2009). In this way, the ACIP's design and operation differ from other models of scientific expert advice used in the federal government (Jasanoff 1990b).

A draft statement withdrawing the ACIP's recommendation for RotaShield was written by senior CDC staff before the October meeting, at which it would be proposed to the committee for approval (CDC 1999c, 184). Wyeth, recognizing from its communications with the CDC that the vaccine's fate was sealed, preemptively withdrew RotaShield from the market on October 15, 1999, one week before the ACIP's scheduled deliberations (Altman 1999b). A Wyeth representative characterized the company's decision to withdraw the vaccine as only a temporary measure, one intended to ensure that the remaining vaccine doses still in the field would not be used while the suspension of vaccination continued (CDC 1999c, 172–75).

One week later, the ACIP's deliberations began with several presentations detailing the methods and results of the safety studies. In his opening remarks, Dr. Livengood made clear the conclusions of his CDC colleagues: "We feel there is a strong causal relationship between rotavirus vaccine and intussusception. It's of high magnitude and it appears to be about one in every five thousand children who are vaccinated with the vaccine" (CDC 1999c, 51).

Following the scientific presentations, the meeting's focus shifted to the implications of those findings. Dr. Roger Glass, a leader of rotavirus activities at the CDC and for years a regular presence during the ACIP's discussions of RotaShield, offered reflections on the decisions facing the committee and the larger public health community regarding RotaShield and the future of rotavirus prevention (CDC 1999c, 148–65). Dr. Glass discussed the ongoing burden of rotavirus-related disease in the United States, the still unresolved questions regarding the relationship between general intussusception rates and the vaccine, and the possibility that vaccination could resume following education of physicians about the diagnosis of intussusception in its early, less severe stages.

Dr. Bernard Ivanoff of the World Health Organization (WHO) followed Dr. Glass, asking the ACIP that its statement on use of the vaccine in the United States leave open the possibility for future testing in countries where risks and benefits with respect to rotavirus and intussusception were vastly different. No questions by or discussion among the committee members followed these presentations and brief remarks by a representative from Wyeth. Instead, the ACIP chair, Dr. John Modlin, directed the discussion to the statement proposed to the committee by the CDC staff. Using the generic name of the vaccine, the critical language of the statement read:

> The Advisory Committee on Immunization Practices, after review of the currently available information from several sources, has concluded that intussusception occurs with significantly increased frequency in the first one to two weeks following vaccination with RRV-TV, particularly following the first dose. Therefore, the ACIP no longer recommends routine immunization of infants with RRV-TV. (CDC 1999c, 178–79)

Notwithstanding Dr. Glass's suggestion that arrangements were possible in which RotaShield could return in the United States, no committee member expressed similar sentiments, nor were objections voiced to the draft statement that would permanently halt vaccination. Members were sympathetic, however, to the international consequences of the new statement. One believed that its wording effectively "slammed the door" to rotavirus vaccination in developing countries in light of the influence of U.S. guidance on international decision making (CDC 1999c, 180).

Committee members and CDC staff discussed language that, while still withdrawing the ACIP's recommendation, might make the vaccine less politically toxic internationally. Dr. Livengood acknowledged the delicacy of the CDC appearing to urge other countries to make decisions that failed to meet the U.S. standard of care. "We try to hint at it, but we try not to say it, in all honesty," he told the committee (CDC 1999c, 182).

Based on this concern for the global consequences of their recommendation, the committee members and agency staff viewed the populations in developing nations that stood to benefit most from RotaShield as what Gutmann and Thompson call "moral constituents" (2004, 37–38). Even though only U.S. residents make up the electoral constituents of federal agencies like the CDC, the participants at the ACIP meeting recognized that the indirect effects of their decision were likely to extend beyond the United States. Through their deliberations, they therefore sought to present and justify their decision in a manner accessible to this global audience.

As discussion continued about adding language to qualify the statement, Dr. Dixie Snider, the CDC's associate director for science and the committee's executive secretary, commented that he had received instructions from the CDC director to have "a statement that is as clear and concise and unambiguous as possible" (CDC 1999c, 184). Dr. Modlin added a moment later, "You can tell we've sort of had our marching orders with respect to the statement" (CDC 1999c, 186).

Dr. Koplan, the CDC director, rejects the suggestion that his instructions to CDC staff may have dictated a particular recommendation from the ACIP membership. "I certainly didn't want a, 'on the one hand, on the other hand, you can do this, you can do that.' The public doesn't like that garbage. They want a clear direction, much like you want from your own doctor" (Koplan 2009). Ultimately, the language in the final, published statement would always be that desired by the CDC, guided in this case by the expressed preferences of the director himself.

The motion to approve the statement as proposed by the CDC staff with minor modifications regarding the renewed importance of rehydration passed without opposition. A *New York Times* story about the announcement described the decision as a "rare and embarrassing reversal" for federal health officials (Altman 1999a). The final statement announcing the withdrawal was published in *MMWR* on November 5, 1999 (CDC 1999f).

Determining the Future of RotaShield in Developing Countries

Even though the fate of RotaShield in the United States had been determined, the future of the vaccine, if any, in developing countries was still unresolved. The ACIP's October meeting demonstrated the shared interest of the committee members and CDC staff in ensuring that U.S. policy regarding the vaccine would not preempt subsequent evaluations of RotaShield internationally (CDC 1999c, 180–84). Whether those efforts were successful would be determined at a three-day meeting on the future of rotavirus vaccine research hosted by the World Health Organization (WHO) in February 2000 (WHO 2000). Among the more than ninety invited participants were prominent experts in rotavirus epidemiology and pathophysiology, including many of the Americans directly involved in the development and regulation of RotaShield. Also present were representatives from global health organizations and health ministers from developing countries.

Since Wyeth had planned to introduce the vaccine to developing nations only after its successful introduction in the United States, very little information was available regarding the safety and efficacy of the vaccine globally. The vaccine had had only limited testing internationally before being licensed in the United States, and the recently started trials coordinated through the WHO had been suspended pending the results of the CDC investigations regarding intussusception.

The meeting considered the global epidemiology of both rotavirus and intussusception; scientific, logistical, and ethical issues related to vaccine clinical trials; and regulatory and supply issues. The meeting concluded with several recommendations developed by the group. Among them was strongly encouraging the development of new rotavirus vaccine candidates, several of which were in early clinical testing (WHO 2000, 46). The group also agreed that further studies of RotaShield in developing countries were ethical, provided that special attention was paid to the diagnosis and treatment of intussusception among research subjects.

While these official recommendations left global health advocates hopeful that the benefits of RotaShield might still be realized, the meeting's participants from the United States left Geneva with little doubt that the vaccine would never be used again. Without data on the vaccine's safety and efficacy in developing countries, the U.S. rejection of RotaShield made the vaccine politically nonviable to health ministers in these nations. At the meeting, American scientists and public health officials in attendance were told by their international counterparts that they could not ask their citizens to accept a vaccine deemed too dangerous for American children, even in countries where as many as 1 in 250 children died from rotavirus-related illness (Allen 2007, 323).

Dr. Albert Kapikian, the NIH scientist whose research led to the vaccine, was told by one health minister, "If it was not good enough for U.S. kids, it was not good enough for their infants either" (Roberts 2004, 1891). Dr. Stanley Plotkin, a distinguished American vaccinologist, pointed out, "No country was willing to place public health above possible criticism for using a vaccine rejected by the United States. This was not exactly a profile in courage" (Allen 2007, 324). Despite the efforts of the CDC and ACIP members to emphasize that their judgments for U.S. policy ought not to be applied elsewhere, their decisions effectively ended any possibility of the vaccine being used internationally.

The outcome of the WHO meeting reveals an additional aspect of inequity in relation to global health, beyond those already reflected in the vastly greater burden of rotavirus disease in the developing world and in the financial and commercial considerations that delayed large-scale global testing of the vaccine. A de facto regulatory inequity was also present, effectively establishing higher barriers for the introduction of the vaccine in developing nations compared with those for wealthy nations.

The scientific and ethical issues related to the testing and potential use of RotaShield in developing countries continued to be debated in the years that followed, even while attention of the rotavirus vaccine research community increasingly turned to next-generation vaccines in development (Coffin and Nelson 2005; Melton 2000; Weijer 2000). The most ardent advocates of RotaShield spoke of the hundreds of thousands of deaths that could have been prevented had the vaccine been available globally between 1999 and the arrival of subsequent rotavirus vaccines starting in 2006.

Such discussions may have been moot because of Wyeth's apparent lack of enthusiasm for continuing testing or distribution of RotaShield following the first warning signs of a possible association with intussusception. In addition to the problems facing RotaShield in 1999, serious safety concerns had also been identified in the company's antiobesity drugs, one of which was used in the combination known as Fen-Phen (Mundy 2001; Whitford 1999). Although the company publicly stated that it had not given up on RotaShield's international potential, it blamed regulatory and health authorities in developing countries for the lack of international testing of the vaccine after the WHO meeting. "You don't do trials with a vaccine that nobody would ever use," Dr. Peter Paradiso, the Wyeth executive who directed the development of RotaShield and was the public face of the company regarding the vaccine, explained in a 2000 interview (GAVI Alliance 2000). (Dr. Paradiso did not agree to be interviewed for this article.)

Dr. Roger Glass, now director of the NIH's Fogarty International Center, believes that the value of the vaccine for global health was never a priority at Wyeth and was even less so after the lucrative U.S. market had been lost:

> To just let this expensive product go off to the Third World for a cheap price was not in their business plan. So while I can say it would have been wonderful to save lives in developing countries, they had no capacity to make this for the developing world, they had no international partners. Thinking internationally was not part of their game plan. . . . While the ethics may sound nice, the economics was the driving force. (2010)

The Politics of Acceptable Risk

Unlike other recent controversies in vaccine safety, RotaShield involved a confirmed, quantified risk associated with a vaccine. Most debates over the safety of vaccines are related instead to hypothesized or alleged risks, such that their very presence is the subject of study and debate. The case of RotaShield therefore provides an uncommon opportunity to examine how known risks and benefits are framed, discussed, and evaluated by the federal officials responsible for public health policy and their expert advisers.

Absent from the public statements announcing the decision to end the use of RotaShield was an explicit comparison of the risks and benefits of continuing vaccination in the United States. While the benefits of RotaShield were more modest in this country than in developing countries, they were significant enough for the CDC to initially recommend the vaccine for all infants. Whether a specific threshold of risk—in either magnitude or severity—was exceeded is not discussed in the *MMWR* statement withdrawing the RotaShield recommendation. The relevant portion of the statement simply states that intussusception occurred with significantly increased frequency following vaccination, and therefore vaccination was no longer recommended (CDC 1999f). The CDC director's preference for a direct, unambiguous statement could explain the absence of a more nuanced analysis articulating the rationale for that decision.

Less easily explained is the absence of a specific discussion regarding RotaShield's risks and benefits during the multi-hour session on the vaccine at the ACIP's October 1999 meeting. Efforts by Dr. Glass to stimulate such an exchange among committee members were unsuccessful. Instead, based on presentations estimating the risk of intussusception because of the vaccine, the committee proceeded directly to considering the wording of the statement proposed by the CDC staff withdrawing the recommendation.

Even if this policy response to the epidemiological data was so evident to the ACIP membership that no other alternative—such as resuming vaccination in tandem with intussusception screening and education programs—warranted even a cursory discussion, there would have been value in explaining the reasoning for that conclusion. Did the frequency of intussusception associated with RotaShield, estimated at the time to be as high as one in five thousand vaccine recipients, surpass a specific threshold that made the vaccine unacceptable? If so, what was that threshold? Was a serious, potentially fatal risk simply unacceptable in the name of prevention, regardless of its likelihood? Did the profile of rotavirus as a minor cause of death in the United States contribute to this conclusion? Since all vaccines present a spectrum of risks to recipients—many minor, some serious—answers to these questions would have been relevant to broader considerations of risk and benefit in vaccination and disease prevention programs.

Answers vary as to why these issues were not discussed by the committee. The CDC's Walter Orenstein believes that the ACIP understood that withdrawal of the recommendation was the only outcome that would be accepted by the CDC, rendering moot any discussion of this option or alternatives. "ACIP members work closely with CDC staff and for the most part get the feeling of what CDC couldn't live with, and I think generally, [they] weren't of a mind to give a recommendation that wouldn't go anywhere" (Orenstein 2009).

Dr. Paul Offit, a member of ACIP at the time and a co-inventor of a later rotavirus vaccine licensed in 2006, regretted that the committee had never had an explicit discussion comparing the risks and benefits of the vaccine, even if the outcome had been the same. The committee chose not to have such a discussion because of fear that it would be perceived by the public as "sacrificing the few for the good of the many," Dr. Offit suggests (2009). "We said this is unsafe for American children, period, without ever defining safety. What we meant by doing it the way we did was absolute safety, which isn't a reasonable definition. It's a lawyer's definition. It's not a doctor or scientist's definition" (Offit 2009).

Dr. Offit, a participant in the February 2000 meeting organized by the WHO, reported on the event at the ACIP's June meeting (CDC 2000). He explained that WHO members had criticized the ACIP for failing to consider the risk-benefit ratio of the vaccine in the United States. They viewed it as a missed opportunity that would have provided a more clear contrast between the context for use of the vaccine in the United States and that in developing countries.

Within months of the end of RotaShield, researchers challenged aspects of the data regarding the association between the vaccine and intussusception (Kapikian 2011). The consensus estimate of the likelihood of intussusception following vaccination eventually declined from approximately 1 in 5,000 to 1 in 10,000 based on better estimates of the overall incidence of the condition (Matson 2006; Peter and Myers 2002). Other researchers estimated the risk at 1 in 32,000 or lower still, theorizing that the cases of intussusception observed shortly after rotavirus vaccination led to a decline in cases later in childhood among "intussusception-prone infants" (Bines 2006; Cohen 2001; B. Murphy et al. 2003).

As challenges mounted to the evidence cited by the CDC to justify its actions on RotaShield, agency personnel offered in 2003 a new, significantly revised, public rationale for its decisions. Writing in the *Journal of Infectious Diseases,* Dr. Trudy Murphy, who directed the 1999 case-control study, and her colleagues explained that "basing decisions solely on the balance of the mortality or morbidity *prevented* by vaccination versus the mortality and morbidity *caused* by vaccination is insufficient" (2003, 1312, emphasis in original). Acknowledging contemporaneous parental concerns about the general safety of vaccines and attention by the media and Congress on this topic, the authors emphasized the importance of making decisions in the best interest of the overall vaccination program, even if those factors led to policy outcomes different from evidence-based evaluations of the measurable risks and benefits of a specific vaccine. Trudy Murphy and her colleagues wrote:

> At a time when many parents express concerns about the safety of vaccines and vaccine adverse events are the focus of increasing attention by the public, media, and U.S. Congress, the wisdom of recommending a vaccine that causes a severe adverse reaction in an estimated 1 in 10,000 infants must be considered. (2003, 1312)

Before the paper by T. Murphy and colleagues was published in 2003, the decision by the CDC staff and advisers to end use of RotaShield had been framed in public statements exclusively using the language of epidemiology. A severe risk associated with the vaccine was identified, confirmed, and quantified, and based on that empirical evidence, scientists and public health experts reached a policy conclusion. With the exception of two passing references to the "current climate" during the June 1999 ACIP meeting, the public discourse regarding RotaShield suggested that its evaluation was isolated from the extremely contentious atmosphere regarding vaccine policy in the United States during this time.

As already noted, developments in 1998/1999 unrelated to RotaShield gave new prominence to safety concerns about vaccines and critics of vaccine policy. Andrew Wakefield's previously discussed paper in *The Lancet* was the most prominent of several hypotheses linking childhood vaccines with autism and other developmental conditions. Attention at this time was also directed toward the potential risks of thimerosal, the mercury-containing vaccine preservative. While thimerosal was not included in RotaShield, officials at the CDC's National Immunization Program were studying both safety controversies concurrently, placing additional strains on agency staff (Wharton 2009). While not acknowledging any risk associated with thimerosal, federal health officials recommended in July 1999 that the ingredient, not required for single-dose vials, be removed from most vaccines.

A personal interest in vaccine safety by Representative Dan Burton (R-IN) ensured that debates over vaccine safety received a still larger platform. Burton, the chairman of the House Committee on Government Reform, had a grandchild with autism that he believed had been caused by vaccines (U.S. Congress 1999, 142). Beginning in 1999, Burton held seven hearings on vaccine safety, at which federal health officials and other advocates of vaccination faced adversarial questioning alleging failures to ensure the safety of vaccines and respond adequately to alleged risks (Colgrove and Bayer 2005). In 2000, alleged conflicts-of-interest related to decision making regarding RotaShield itself became a focus of the committee (U.S. Congress 2000).

Serious concerns regarding vaccine safety had been an occasional presence throughout the prior half century of vaccination activities in the United States. Within weeks of the eagerly anticipated arrival of Jonas Salk's polio vaccine in 1955, manufacturing failures by Cutter Laboratories exposed thousands of children to live polio virus, leading to ten deaths and many more cases of paralysis (Offit 2005). In 1976, a nationwide mass immunization program launched after an outbreak of swine influenza at a New Jersey military base was halted after cases of Guillain-Barre Syndrome, a neuromuscular disorder, were observed among vaccine recipients (Neustadt and Fineberg 1978). In the early 1980s, allegations of neurodevelopmental risks of the pertussis component of the diphtheria-tetanus-pertussis combination vaccine led to lawsuits against vaccine manufacturers, the creation of parent-led vaccine safety organizations, and the establishment of a federal vaccine injury compensation program (Colgrove 2006, 208–17). National vaccination efforts had survived each of these past controversies, but the multifront attack on vaccine safety in 1999 led senior CDC officials to believe that without decisive action to preserve public support for vaccines and vaccine policymakers, the entire U.S. immunization program would be at risk (Koplan 2009; Orenstein 2009).

In their 2003 retrospective piece, Trudy Murphy and her colleagues wrote, "Public confidence and the support of vaccine providers for vaccination recommendations, although difficult to quantify, are important factors in the decision-making process" (2003, 1312). Consistent with this argument, former leaders at the CDC now acknowledge how the crisis facing national vaccination efforts in 1999 shaped the fate of RotaShield in ways not articulated publicly at the time. Jeffrey Koplan and Walter Orenstein knew that their critics were alleging that the CDC cared more about vaccine promotion than vaccine safety, and RotaShield was a vaccine with a known, serious risk. "This was not viewed as rotavirus simply for rotavirus's sake but also the potential for maintaining public faith and credence in the overall immunization schedule," Dr. Orenstein explained (2009).

According to Dr. Koplan, "In the context of a U.S. population with a severe side effect occurring rarely but in a measurable way in very young children, public perception issues drove it as much as the benefit" (Koplan 2009). For critics who lament the absence of an explicit comparison of risks and benefits at the ACIP's October 1999 meeting, the failure to consider redesigned vaccination programs that would mitigate risks, or the accuracy of the estimates of intussusception attributable to the vaccine, these retrospective statements clarify why such arguments were inconsequential to the ultimate fate of the vaccine.

A quantitative threshold of acceptable risk was never identified for RotaShield, but a qualitative threshold was unmistakably passed. This threshold was not expressed in terms of disease prevented compared with intussusceptions caused but as a threshold reflecting political viability and public perception. The epidemiological research conducted in the summer of 1999 clearly contributed to the decision to end use of the vaccine. However, the public justifications at the time relied exclusively on those technical, quantitative arguments regarding the vaccine's risks, with no direct acknowledgment of the critical role of value judgments and societal concerns that were at least as influential in the ultimate policy conclusion (Jasanoff 1990a).

The role of external considerations and social values in public health regulation and policy has been well documented, particularly in areas requiring the identification and assessment of risks (Gostin 2008; Gray and Ropeik 2002; Oliver 2006). Since perceptions of risk and their policy implications often vary widely among policymakers, scientists, and the public, expert bodies like the ACIP have long been consulted in efforts to determine acceptable levels of risk, to identify what constitutes "safety," and to offer other related judgments (Cross 1994; Fischhoff et al. 1981; Lowrance 1976).

The RotaShield story demonstrates the difficulties faced by public health policymakers and their expert advisers in confronting, directly and publicly, issues related to values and public perception when deciding the future of RotaShield. Instead of explicitly engaging with these inherently subjective concerns, those involved in the fate of the vaccine initially relied on the perceived objectivity associated with quantitative data, continuing a trend toward quantification observed throughout modern science (Porter 1995). Only after justifications based on numerical measures of risk and benefit were shown to be inadequate did public accounts of RotaShield decision making retrospectively acknowledge the significance of qualitative concerns such as the preservation of public confidence in vaccination and perceptions regarding the risk acceptable as part of disease prevention.

Rotavirus Vaccines and Intussusception Revisited

Following the end of RotaShield, the future of rotavirus vaccine research was uncertain. Other rotavirus vaccine candidates remained under development by competing pharmaceutical manufacturers, but experts worried that the experience with RotaShield and intussusception might lead those companies to abandon their rotavirus vaccine programs (Roberts 2004).

Two vaccines were in late-stage development by 2004, developed separately by Merck and GlaxoSmithKline (GSK). Since the precise mechanism explaining how RotaShield caused intussusception was not known, the FDA required manufacturers to show, before licensure, that the condition was not also caused by their products (Clark et al. 2008). This required clinical trials vastly larger than the 10,000 subjects who participated in the testing of RotaShield, a number that had been insufficient to identify the link to intussusception with statistical confidence. Merck's vaccine, RotaTeq, was tested in 70,000 children, and the GSK vaccine, Rotarix, was tested in 63,000 children (Offit and Clark 2011).

Requirements for studies this large prompted manufacturers to conduct trials in developed and developing countries simultaneously, providing an earlier, broader view of the vaccine's safety and efficacy internationally than was available for RotaShield (Glass et al. 2004). Both vaccines were shown to be safe and effective in clinical testing, with no evidence suggesting an association between either vaccine and intussusception (Clark et al. 2008, 726, 729). RotaTeq was licensed in the United States and recommended for routine use in infants in February 2006, and Rotarix followed in June 2008.

Postlicensure safety monitoring of both vaccines has since detected small associations with intussusception. For Rotarix, the estimated risk is 1 in 51,000 to 68,000 vaccinated infants, at least five times lower than the risk seen with RotaShield (Patel et al. 2011). In response to these data, both the CDC and the WHO reaffirmed their recommendations that all infants in the United States and worldwide be vaccinated, explaining that the demonstrated benefits of the vaccines greatly outweigh the risk of intussusception (CDC 2011; Glass, Patel, and Parashar 2011; Greenberg 2011; WHO 2011). Efforts to further study and introduce these vaccines as well as other novel rotavirus vaccine candidates continue worldwide.

The disparate responses to intussusception fears for these newer vaccines compared with RotaShield, particularly the explicit references to risk-benefit comparisons in statements by health officials, lend credence to arguments that the timing of events surrounding RotaShield determined its fate as least as much as did the epidemiological evidence cited at the time. Unlike these relatively well-established second-generation vaccines, RotaShield was only months old at the time the intussusception fears emerged, making its risks far more visible than its benefits to health care providers and the public. With the newer vaccines, substantial evidence of benefits was available by the time concerns about intussusception appeared (Curns et al. 2010; Tate et al. 2011b). For RotaShield, such benefits were anticipated but had not yet been demonstrated outside the clinical research setting when intussusception cases were first reported. Regarding the broader climate of vaccine policy in the United States, safety controversies persist, but the crisis of alarm and uncertainty experienced during the late 1990s has calmed somewhat in recent years.

RotaShield and Public Health—Looking Back, Looking Ahead

Retrospective studies of RotaShield have estimated that approximately 1 million doses of the vaccine were administered to just over 500,000 children during its brief time in use, considerably less than initial estimates (Smith et al. 2003). A total of 112 reports of intussusception temporally linked to the vaccine were submitted to VAERS, and 98 were confirmed by subsequent review of medical records or interviews with health care providers (Zanardi et al. 2001). Surgery was required in just over half the cases, and one case was fatal, a five-month girl whose death was attributed to hypovolemic shock caused by intussusception and resulting bowel necrosis (Zanardi et al. 2001). Attempts to understand the precise mechanism by which RotaShield caused intussusception have resulted in several proposed etiologies but no confirmed conclusion (Clark et al. 2008; Lynch et al. 2006).

Even as the attention of the global health community has long since turned to the implementation of the two subsequently licensed rotavirus vaccines or the development of still newer vaccines, a small cohort of scientists continue to believe that RotaShield could return as a viable public health intervention. The International Medica Foundation (IMF), its current rights-holder, argues that RotaShield could be a safe, effective, and less expensive option for the prevention of rotavirus (IMF 2011). As of the spring of 2011, a phase II clinical trial of the vaccine was under way in Ghana (Glass 2010).

For most people, however, the RotaShield story is now exclusively a chapter in the history of public health and vaccination programs. Officials at the CDC have embraced, even encouraged, efforts to highlight the historical significance of the events culminating in the removal of the vaccine. In a 2004 retrospective item in *MMWR* about the suspension and investigation of RotaShield, the authors—participants in those events several years earlier—favorably compare their actions with those of John Snow and the Broad Street pump, a legendary episode in the early history of epidemiology (CDC 2004; Porter 1997). "Both were decisive, life-saving public health actions," the authors write. The report concludes, "The rapid elimination of risk based on systematic investigation, surveillance, and ongoing scientific confirmation averted any other cases of intussusception associated with [RotaShield]" (CDC 2004, 789). Unlike the 2003 publication by CDC personnel responding to critics, the role of external factors, broad policy considerations, and public perception is once again absent from this telling of the RotaShield story.

The concept of the "elimination of risk" and the larger comparison of RotaShield and Snow's actions in 1854 are deeply flawed. The challenges for scientists and policymakers when investigating and responding to a risk associated with a vaccine or other medical interventions are far more difficult than identifying the source of a communicable disease outbreak. While the RotaShield investigational studies followed the methodological traditions that epidemiologists trace to Snow, the CDC authors conflated the suspension, investigation, and withdrawal of the vaccine into a single, continuous event. The result is the implication that the decision to permanently halt use of the vaccine was as obvious as Snow's closing of the Broad Street pump that brought cholera-contaminated water to London. It ignores the spectrum of risks *and* benefits for public health interventions like vaccination that make the translation of evidence into policy considerably more difficult.

The concept of the "elimination of risk" also obscures the trade-offs related to the risks and benefits inherent in any medical intervention, including preventive measures such as vaccination. While the removal of RotaShield did eliminate the risk of intussusception, another class of risks, those of rotavirus itself in the United States and worldwide, continued unabated for years. It implies an untenable standard for policymakers, health care providers, and the public when evaluating the risks of preventive or therapeutic interventions, one that contradicts long-standing risk communication efforts by health officials and advocates.

Overall, the legacy of the RotaShield story is surely one highlighting the ability of vaccine safety surveillance mechanisms to identify quickly a possible adverse event warranting further investigation, as is often noted. It is also a demonstration of the ability of the U.S. public health community to marshal resources and energies in order to quickly and conclusively confirm the existence of a safety concern through epidemiological research. The legacy of RotaShield is likewise seen in larger prelicensure clinical trials more likely to detect rare adverse events for newer vaccines and earlier attention to studying vaccines in all populations that could benefit.

Enthusiasm for evidence-based decision making is prevalent throughout medicine and public health. The "evidence" referred to in this context is overwhelmingly quantitative evidence, such as data from outcomes research, experimental findings, and economic modeling. Another legacy of the RotaShield story should be greater explicit attention to the processes by which individuals with decision-making responsibility—in this case, CDC officials and their expert advisers—evaluate this evidence and translate it into regulation and policy. While quantitative evidence is essential to determinations of safety, effectiveness, cost-effectiveness, and thresholds of acceptable risk, conclusions in each of these areas ultimately and unavoidably require qualitative, subjective assessments to be made.

The RotaShield story highlights the role of external considerations, political pressures, and social values in the translation of evidence into policy by health officials and their expert advisers. It also shows how these classes of concerns, while unmistakably important to those evaluating RotaShield, were all but absent from their public discourse regarding the fate of the vaccine until years later. In their place were narrow, technical justifications that failed to provide a more complete rationale for the decisions to the American public and, just as important, to the international health community. As the quantitative tools available to enhance health decision making become ever more sophisticated, comparable attention to the processes by which individuals must interpret and act on such evidence will be increasingly essential to best promoting the health of individuals and populations worldwide.

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