Pediatrics rescinded the recommendations for RRV in October 1999, and the manufacturer thereupon withdrew the vaccine from the market and ceased production (57,58). The association with intussusception was not detected in the pre-licensure studies because the sample size was inadequate to detect such a rare adverse event (109). Two other manufacturers persevered with the development of other candidate vaccines and conducted multicenter phase III trials with 30,000 to 35,000 vaccine recipients and equivalent numbers of placebo recipients who received vaccine at more restricted early ages (59,60). Neither vaccine was associated with an increased occurrence of intussusception, and both vaccines have been approved for use. This experience highlights the need for conducting trials to address safety questions for some vaccines that are much larger than the size needed to evaluate efficacy. Also, all vaccines of the same type may not have the same safety profile, emphasizing the need for post-licensure studies to identify adverse events that might occur at rates too infrequent to be detected prior to licensure in clinical trials.

Osp A Lyme Disease Vaccine

In 1998 a vaccine containing the Osp A protein of *Borrelia burgdorferi* was licensed on the basis of demonstrated efficacy and no significant increased risk of serious adverse events (61). A similar product developed by another manufacturer was also shown to be efficacious and without serious adverse events (62). Shortly before licensure, studies of patients with treatment-resistant Lyme arthritis indicated a possible cross-reactive amino acid sequence in the Osp A protein with human leukocyte functional antigen (63). Although there was no evidence of increased risk of arthritis following vaccination in either the pre-licensure or the post-licensure safety data, concerns about this possible association undoubtedly tempered the recommendations for use of the vaccine by advisory committees and resulted in limited sales. In addition, class action lawsuits were filed and settled out of court. The manufacturer withdrew the licensure for the vaccine in 2002. Concerns about possible cross-reactivity with vaccine components have hindered the development of other vaccines based on components of bacteria that could theoretically trigger autoimmune disorders including group A streptococci (64) and group B meningococci.

FALSE PERCEPTIONS OF SAFETY

Concerns about vaccine safety can reduce the acceptance of immunizations with consequent outbreaks of vaccine-preventable diseases even when the scientific data do not support a causal relationship. Alleged links between measles, mumps, and rubella (MMR) vaccine and inflammatory bowel disease and autism were made on the basis of very weak anecdotal observations (65,66). Careful reviews of these hypotheses found them to be without merit (67,68). The concerns, however, resulted in decreased acceptance of MMR in Great Britain and outbreaks of measles (69). In 1999 the U.S. Public Health Service and the American Academy of Pediatrics called for a reduction or removal of thimerosal as a preservative from vaccines administered to infants because the potential cumulative exposure exceeded guidelines for exposure to methylmercury (70,71). After preliminary data suggested the possibility of an association with neurodevelopmental disorders, some groups believed that thimerosal might cause autism (72). Subsequent epidemiological studies and careful evaluation for neurodevelopmental disorders at 7 to 10 years of age have revealed no consistent evidence of any substantial neurodevelopmental disorder associated with thimerosal exposure (73,74). The complexity of these issues points to the need for a comprehensive and systematic approach to evaluating data on vaccine safety. New issues and concerns arise regularly, indicating the need for ongoing programs to address safety concerns.

VACCINE SAFETY ACROSS THE LIFE CYCLE

At the earliest stages of development, vaccine researchers should develop a comprehensive plan to acquire necessary data on safety and efficacy during all phases of development. Numerous judgments will be required as to the type and quantity of safety data required to support licensure, including preclinical toxicity testing and sample size of clinical studies. The required data will differ for a vaccine intended for universal use in children as compared with one to be used in more niche populations such as adult travelers.

Depending on the product class, some potential safety concerns are known a priori or can be predicted from the historical experience of development of similar vaccines. Understanding the background incidence of illness occurring in the target population and anticipating risks that might be perceived as related to vaccination may be as important as understanding the product-related risks, because ultimately the intended population will need to be convinced that the vaccine is safe enough to use. The developer can begin this process by identifying the diseases in the target population that might be suspected to be related to the vaccine because onset or diagnosis may coincide with the timing of immunizations. Neurological, rheumatological, and other immune-mediated disorders have been falsely attributed to vaccines when other etiologies could not be established. In addition, disorders that are not well understood but have occurred with some temporal relation to immunization, such as sudden infant death syndrome or Gulf War syndrome, have also been linked with immunization in the minds of the public even though the scientific data do not support a causal relationship. Developers should decide whether it is necessary to develop evidence that the vaccine does not cause a particular condition when such perceptions may affect public acceptance of the vaccine. Ultimately, safety assessments should provide adequate data to support licensure and recommendations for use as well as communicating the benefits and risks of the vaccines.

Responsibility for evaluating vaccine safety begins with vaccine researchers and/or manufacturers and later extends to regulatory authorities, other government and international agencies, immunization advisory bodies, and health care providers. Much attention has been devoted to immunization safety efforts in the last decade in the United States and worldwide. The WHO has made immunization safety a global priority (75,76). The International Conference on Harmonisation (ICH), a collaborative effort of regulatory authorities and pharmaceutical companies in Europe, Japan, and the United States to harmonize requirements for registering pharmaceutical products, has developed recommendations on a range of preclinical, clinical, and post-licensure safety evaluations (77).

Safety, as defined by the FDA, is ''the relative freedom from harmful effect to persons affected directly or indirectly by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time'' (78). Thus, safety is *relative* and *relational*; it depends on the benefit/risk assessment at a particular point in time, the specific indication, and the intended recipient.