in Queensland, Australia following contamination of a multidose container of diphtheria toxin-antitoxin mixture, prompting the investigating committee to recommend that biological products should not be formulated in containers for multiple use unless a sufficient concentration of antiseptic was added to inhibit microbial growth (36). The contamination of yellow fever vaccine with hepatitis B virus and polio vaccines with SV40 virus indicate the need for careful quality control of all materials used in the manufacturing process.

Seed Lots and Standardization of Manufacturing

Prior to 1947, yellow fever vaccines were maintained in laboratories and produced as needed in different cell lines on the basis of availability. The demonstration of marked variability of the risk of encephalitis associated with different lots of vaccine in Brazil demonstrated the need for standardizing manufacturing procedures to assure that all lots of live, attenuated viral vaccines have the same characteristics (37,38).

The Cutter Incident

In 1955 rapid scale-up of production was required to meet projected demand for inactivated polio vaccine (IPV). Certain lots of vaccine produced by one manufacturer had incomplete inactivation of viruses due to aggregates of poliovirus. Sixty cases of paralytic polio occurred in vaccine recipients, and 89 cases in family contacts in the so-called ''Cutter incident'' (39,40). This incident highlighted the importance of quality control for every change in the manufacturing process and careful monitoring of vaccine safety post licensure.

Vaccine-Associated Paralytic Polio and Vaccine-Derived Polio Outbreaks

In 1964 the Public Health Service commissioned a special advisory committee to evaluate a small number of cases of paralytic polio following receipt of oral polio vaccine (OPV) in vaccinated individuals living in non-epidemic areas. Because no laboratory techniques were available at that time to distinguish vaccines from wild-type polio strains, the committee relied on epidemiological surveillance data between 1962 and 1964. The epidemiological evidence pointed to a causal link with OPV (41). Subsequent developments of laboratory methods, including genetic sequencing, now clearly differentiate wild-type from vaccine-derived polioviruses (42). OPV causes vaccine associated paralytic polio (VAPP) in the recipient or a close contact (43). OPV can also revert to a wild-type phenotype and cause outbreaks of circulating vaccine-derived polioviruses (cVDPV) (44). Also, persistent excretion of polio vaccine viruses for many years can occur in immunodeficient persons and later be transmitted to susceptible persons (44).

Enhancement of Measles and Respiratory Syncytial Virus Disease Following Formalin-Inactivated Vaccines

Infant recipients of an investigational formalin-inactivated respiratory syncytial virus (RSV) vaccine developed more severe lower respiratory disease and were more likely to be hospitalized than unvaccinated infants after exposure to RSV many months after vaccination (45,46). Also, some children who received a licensed inactivated measles vaccine developed ''atypical'' and more severe respiratory disease than unvaccinated children two or more years later when they were exposed to wild-type measles virus (47,48). The measles vaccine had been licensed in 1963 on the basis of safety and immunogenicity data as well as demonstrated protective efficacy following exposure to measles in the one year following vaccination. These experiences demonstrated the potential for serious adverse events to take place years after vaccination even with vaccines produced in a manner similar to other successful vaccines without such adverse events (i.e., IPV). These vaccines induced poor-affinity antibody, and protection waned after several months. The enhanced pulmonary disease was caused by antigen-antibody complexes (49). Understanding the pathogenesis of adverse events and development of an animal model open the door to evaluating new candidate vaccines.

Whole-Cell Pertussis Vaccines

During the 1970s and 1980s, concerns were raised, first in Japan and Europe and later in the United States, over a possible association between encephalopathy and DTP vaccine (diphtheria and tetanus toxoids and whole-cell pertussis vaccine combination) (50,51). Whole-cell pertussis vaccination was discontinued in Japan and not recommended in Sweden, and some U.S. vaccine manufacturers withdrew from the marketplace, creating the potential for vaccine shortages. A coalition of health professional organizations, consumer advocacy groups, and others pressed for the passage of the National Childhood Vaccine Injury Act of 1986 (52). The Act created the VICP, called for unifying national reporting system for adverse events [the Vaccine Adverse Event Reporting System (VAERS)], mandated comprehensive reviews of vaccine-related adverse events by the Institute of Medicine (IOM), provided for improved record keeping of vaccine administration, and mandated the development and distribution of vaccine information materials. Acellular pertussis vaccines were first developed and marketed in Japan. Comparison studies demonstrated efficacy for several acellular vaccines comparable to or higher than whole-cell vaccines, and the acellular products were associated with reduced rates of fever, febrile seizures, local swelling, tenderness, and pain associated with whole-cell products (53). Acellular products have replaced whole-cell vaccines in most industrialized countries, but highly effective whole-cell vaccines continue to be used in many developing countries, primarily because of the lower cost than that of acellular products. The experience with whole-cell vaccines in industrialized countries highlights the importance of public acceptance of vaccines and the need to make vaccines as safe as possible to maintain public confidence.

Rotavirus Vaccines

RRV (Rotashield®) was licensed in 1998 on the basis of demonstrated efficacy and safety in several trials. Intussusception was observed during pre-licensure clinical studies in 5 out of 10,054 (0.05%) infants who received RRV and 1 out of 4633 (0.02%) placebo recipients ($p > 0.45$) (54). Following licensure, reports to VAERS of nine children who developed intussusception after receipt of RRV led to an initial case-control study and a recommendation to temporarily suspend use of the vaccine (55). Case-control/case-series and retrospective cohort studies showed the association between RRV and intussusception to be strong, temporal, and specific, with the attributable risk estimated to be approximately 1 in 5000 to 1 in 11,000 vaccine recipients (25,56). The Advisory Committee on Immunization Practices (ACIP) and the American Academy of