Anatomy of a Global Sentinel Event: Vaccine Safety in Vietnam

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INTRODUCTION
May 10, 2006, seemed like a typical spring day at Children’s Hospital No. 1 (CH1), one of the two tertiary-care pediatric hospitals that serve Ho Chi Minh City (formerly, Saigon) and the regional referral center for southern Vietnam. Nurses attended to their inpatient charges, anxious parents lined the corridors, and the usual crowd of fidgeting babies and nervous toddlers awaiting outpatient appointments had already swamped the reception halls.

Atop the usual tumult, a situation was brewing that would have tragic consequences for one family; deeply reduce national immunization rates; and have global implications for the secure transport, safe storage, and appropriate administration of vaccines. The unfolding of events that sadly culminated at Children’s Hospital and the subsequent national and international investigations reveal much about how governments, public health officials, and disease investigators can cooperate to identify the source of a lethal disease, halt its spread, and correct variations from safe practices that are designed to protect children.

SERIOUS ILLNESSES IN VACCINATED CHILDREN
As the hospital’s morning rush settled into its afternoon routine, a 13-month-old boy was brought to the emergency department with an alarming pattern of symptoms: fever, a swollen left arm, tachycardia, hypotension, and lethargy. A few hours later, another 13-month-old boy arrived with a similar, but even more severe, constellation of symptoms. Septic shock was the diagnosis in both cases. Immediate intensive interventions followed. Despite aggressive resuscitation, the second child died of multisystem organ failure.

Within hours, four more children arrived with the same ominous pattern of symptoms. In less than 48 hours, six children had been admitted with the same initial symptoms and a rapid progression to multisystem organ failure. All of the children were intubated, multi-site specimens were obtained for culture, and inovavenous antibiotics were given. One troubling fact was common in all the case histories: each child had received Priorix (GlaxoSmithKline) measles–mumps–rubella (MMR) vaccines. The unfolding of events that sadly culminated at Children’s Hospital and the subsequent national and international investigations reveal much about how governments, public health officials, and disease investigators can cooperate to identify the source of a lethal disease, halt its spread, and correct variations from safe practices that are designed to protect children.

LOOKING FOR THE CAUSE
Alerted by this cluster of nearly identical cases and shared histories, physicians caring for the children began a sequence of notifications. The first notice was sent to the nation’s Ministry of Health’s National Inspection Center for Vaccines and Medical Products to review the cases; advised GlaxoSmithKline of the death and illnesses; and suspended the manufacturer’s MMR vaccines from the national vaccination program.

With overtones that initially faulted the vaccine, newspaper and television reports featured the suspension, and hospitals and clinics stopped using Priorix. Some clinics and hospitals even voluntarily stopped all vaccinations—a decision that the Ministry of Health had neither advised nor supported.

GlaxoSmithKline quickly wrote to the Ministry of Health, advising that the illness pattern was unlike any known side effects of Priorix and that non–vaccine-associated problems could be the cause of the illnesses. Nevertheless, the company advised its Vietnam distributors to hold all stocks of the vaccine and sent immunization consultants from Belgium to help with the investigations. Recognizing the global implications of vaccine-borne illness, the World Health Organization also sent vaccination specialists to join the investigation.

Initial blood cultures from the affected children grew Staphylococcus aureus. Sensitivity testing showed methicillin resistance. This finding, as well as the rapid multisystem progression of symptoms, led to a diagnosis of toxic shock syndrome. Additional blood cultures were sent to an Oxford Wellcome Trust laboratory in Thailand for a confirmatory analysis.

Family members of the affected children and other contacts were traced. All of the tracings intersected at the District 5 Health Center of Ho Chi Minh City, where all of the hospitalized children had been vaccinated by the same staff member. Nasopharyngeal samples were obtained from the vaccination team, and methicillin-resistant S. aureus (MRSA) was detected. Genomic subtyping was completed at the Wellcome Trust-supported Hospital for Tropical Diseases in Ho Chi Minh City, and a match of the pathogen in the hospitalized children was confirmed.

A direct link was established, but the method of causation was unclear. Early reports stated that the vaccination team wore gloves, followed the usual hygienic techniques, and had no known illness during the days on which the children were vaccinated. Confirming the validity of these reports may be the most challenging step of all, because a discrepancy remains between the staff’s statements regarding good hygiene and the transfer of MRSA from a vaccinator to the children.

Meanwhile, contributory factors were also pursued. GlaxoSmithKline confirmed no reports of similar illness in vaccinated children in other nations that were using Priorix, and assays of archived vaccines contained no contaminants. In Vietnam, the Ministry of Health secured the remaining stocks of the vaccine. Tests were conducted on samples from the stock under recommended storage conditions and under replicated unsafe storage conditions.
Product bioassays were performed, and responses to injections of the vaccine in animal models were assessed. Neither in vitro contamination nor untoward in vivo responses were reported. Although Priorix was still embargoed by the Ministry of Health at the time this article went to print, the vaccine itself appears to have been exonerated.

This has not been the case with the vaccine supply chain. Providing vaccines is challenging in Vietnam. Foreign manufacturers are not permitted to import or distribute their products directly. Instead, Vietnamese importers and distributors must be used. Each transfer of product between manufacturer, importer, distributor, storage facility, and end-user is an opportunity for substandard or illicit practices to erode vaccine safety. In this case, it appears that there were irregularities in transferring the product, but whether these contributed to the children’s illnesses is unclear.

Ministry of Health regulations state that vaccines must be stored and transported in accordance with the manufacturer’s guidelines. Adherence to the guidelines is enhanced when imported vaccines are held at one of four approved cool storage centers. From these centers, the vaccines are distributed to cool store warehouses, as approved by the provincial health authority, and are then sent to refrigerated units at district health centers.

When handled by mobile vaccination teams, the vaccines are carried to their final destinations in chilled containers. The goal is to keep the vaccines at temperatures that inhibit decomposition (i.e., from 2° to 8° Celsius).

Of 109 Priorix doses delivered from a private cool storage center to the district health center, 64 doses were used immediately. Forty-five doses were given over the next three weeks, including 13 doses that were given 12, 13, and 14 days after being received. At the time of publication, the storage conditions of these doses were unreported. The six hospitalized children had received their vaccinations during these days. The remaining 23 doses were recovered and used in subsequent testing, as described earlier.

From the initial reports, it appears that the vaccines administered to the stricken children were stored and transported outside of state controls (but not necessarily outside of recommended conditions). Nine days after the sentinel event at Children’s Hospital, Ho Chi Minh City health department officials raided the offices of the private Vietnamese vaccine distributor. While checking the company’s legal status, the officials determined that the company’s five-year eligibility to trade in vaccines and immune biologic products had expired several months earlier. The company countered that it had passed a Ministry of Health inspection just weeks before the illnesses occurred. Furthermore, its Ministry of Health certificate to trade in vaccines had no expiration date.

This type of confusion over the legal status of companies within drug channels is not unusual. Regulations are complex, enforcement may be multijurisdictional, and cabotage (the exclusive right of a country to control transport within its territory) is vulnerable to extortion.

CRISES IN CONTEXT: SHADES OF THE EARLY 20TH CENTURY

The presentation of the illnesses, their selectivity for recently vaccinated children, and the findings of irregularities in drug transport, storage, and documentation are eerily similar to two historical events that have substantially influenced the development and use of vaccines and other biological agents.

Tetanus in 1901

In 1901, a former milk wagon horse had been used to produce sera containing antibodies to diphtheria toxin. In October of that year, the horse developed tetanus and was killed. Unfortunately, diphtheria toxin serum from the horse, dated September 30, 1901, had been incubating tetanus and was unwittingly used in vaccination programs. A young girl in St. Louis subsequently died of tetanus.

In the absence of clear regulatory guidance or uniform controls, samples from September 30 were used to fill bottles labeled August 24, 1901. These samples of antitoxin—which were thought to be free of contamination—were distributed and caused the deaths of 12 more children.

Prompted by this incident, President Theodore Roosevelt signed the Biologics Control Act of 1902, which established the Center for Biologics Evaluation and Research (CBER), one of the five main centers that four years later become the U.S. Food and Drug Administration (FDA).1,2

Toxic Shock Syndrome in 1928

The second event was even more similar to the incident in Vietnam. It involved vaccine-associated deaths from S. aureus-mediated toxic shock syndrome. In 1928 (the year penicillin was discovered), 12 children in Bundaberg, Australia, died shortly after receiving injections of diphtheria vaccine.

An investigation by an Australian Royal Commission, headed by a future Nobel Prize–winning immunologist, found that the vaccine had become contaminated by S. aureus. The bottle containing the vaccine had been stored at room temperature for a week before the vaccines were given. There was confusion as to who was accountable for the safe storage and use of the serum, and the vaccine’s convoluted pedigree made attributing responsibility nearly impossible.

As a result of its findings, the Royal Commission recommended that all vaccines packaged in containers containing multiple doses must incorporate an antibacterial preservative.3 At the time, the optimal preservative was determined to be thimerosal, a chemical that would later acquire its own infamy.

In a cruel twist of fate, a score of people recently died of medically acquired S. aureus infections—again in Bundaberg.4-7 Most cases have been attributed to a single surgeon’s substandard hygiene practices—a concern not fully dismissed in the Vietnam incident.

UNINTENDED CONSEQUENCES

In Vietnam, one unfortunate result of the publicity surrounding the pediatric death and illnesses has been the diminished confidence of patients regarding drug and vaccine supplies. This certainly occurred immediately after the announcement of the illnesses at Children’s Hospital. Within days, the overall vaccination rate at Ho Chi Minh City’s children’s hospitals and private clinics was halved. This sharp drop was so concerning that five weeks after the first case was publicized, doctors from the Ministry of Health’s National Extended Program on Immunization, GlaxoSmithKline, and the Pasteur Institute joined
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together to encourage parents to adhere to recommended vaccination schedules for their children. (It is interesting that the physicians also urged health care workers to follow hygienic protocols and adhere to the requirements regarding storage conditions.)

INTERNATIONAL COOPERATION

This multiorganizational, multinational cooperative effort appears to be working. Vaccination rates are heading back toward the pre-May 10 levels. It is possible that the government’s willingness to work with several layers of domestic and international organizations and to publicly account for problems within the vaccine distribution and administration system will eventually increase public confidence well beyond any previous levels.

The scientific investigation that identified the source of a lethal illness reveals how infections with worldwide implications are recognized, confirmed, and controlled. The communication and cooperation that characterized the response to this event lends insight into how governments that were once conditioned to dealing with problems through obscure internal mechanisms can more openly engage international assistance to build a safer health care system.

REFERENCES