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Outbreaks of Group A Streptococcal Abscesses Following Diphtheria-Tetanus Toxoid-Pertussis Vaccination

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ABSTRACT: Two outbreaks of group A streptococcal abscesses following receipt of diphtheria-tetanus toxoid-pertussis (DTP) vaccine from different manufacturers were reported to the Centers for Disease Control (CDC) in 1982. The clustering of the immunization times of cases, the isolation of the same serotype of Streptococcus from all cases in each outbreak, and the absence of reported abscesses associated with receipt of the same lots of vaccine in other regions of the country, suggest that each outbreak was probably caused by contamination of a single 15-dose vial of vaccine. The preservative thimerosal was present within acceptable limits in unopened vials from the same lot of DTP vaccine in each outbreak. Challenge studies indicate that a strain of Streptococcus from one of the patients can survive up to 15 days in DTP vaccine at 4 degrees C. Contamination of vials during manufacturing would have required survival of streptococci for a minimum of 8 months. Preservatives in multi-dose vaccine vials do not prevent short-term bacterial contamination. Options to prevent further clusters of streptococcal abscesses are discussed. The only feasible and cost-effective preventive measure now available is careful attention to sterile technique when administering vaccine from multi-dose vials.

[streptococcal abscesses; abscesses; diphtheria-tetanus toxoid-pertussis (DTP) vaccine; vaccine reactions.]

TEXT:

Commonly reported reactions following diphtheria-tetanus toxoid-pertussis (DTP) vaccination have included redness, swelling, and pain at the injection site and systemic symptoms of fever, drowsiness, fretfulness, vomiting, anorexia, and persistent crying. Less commonly reported reactions have included convulsions and hypotonic hyporesponsive episodes. [n1] Sterile abscesses at the site of injection have been reported to occur at a rate of about ten per million doses of presently available DTP vaccines. [n2] Pyogenic abscesses have been an unusual complication of DTP vaccination [n3] and streptococcal abscesses have rarely been reported. [n4-n6]

Two clusters of streptococcal abscess after DTP vaccination were investigated in Georgia and Oklahoma in 1982. We report the epidemiologic and laboratory investigations of these two outbreaks and their policy implications.

BACKGROUND

These outbreaks occurred in two private pediatric practices, one in a northern Atlanta metropolitan area and the other in a small community in Oklahoma. DTP vaccine is purchased in 7.5-mL multi-dose vials, which are stored at 4 degrees C until used. Vaccine vials are usually kept at room temperature during the hours of immunization; vaccine is not left at room temperature for more than three hours. Thirteen to 14 doses of vaccine are usually obtained from each vial.

Only the nurse administer vaccine. Procedures of vaccine administration were the same in each practice except for the use of alcohol-soaked cotton balls in the Atlanta practice and the use of disposable alcohol wipes in the Oklahoma practice to disinfect the stopper of the vaccine vial and clean the injection site.

MATERIALS AND METHODS

A case definition was established of abscess appearing at the injection site within 2 weeks of receipt of vaccine. Names, addresses, and telephone numbers of parents of all children immunized with any vaccine on the days of apparent risk (July 19 and 20, 1982, in the Georgia outbreak and October 15 and 18, 1982, in the Oklahoma outbreak), and for a few days before and after the high risk period, were obtained from physician records. These parents were interviewed by telephone to establish the approximate time of vaccination, to identify the nurse administering vaccine, and to characterize the nature and extent of reactions following immunization. Physician and hospital records of cases were reviewed to characterize the clinical presentation and treatment of these abscesses; additional data on costs were obtained in the Georgia outbreak. Serotyping of all streptococcal isolates was done at the Centers for Disease Control (CDC).

All nursing personnel (and the physicians in the Oklahoma outbreak) were interviewed to obtain information about recent illness. Swabs for bacteriologic culture were taken (on July 30 in Georgia and on October 26 and 28 in Oklahoma) from scalp, throat, rectum and vagina, and from any skin lesions. Follow-up throat swabs for bacteriologic culture were taken from children who had been seen for a complaint of sore throat just prior to the outbreaks and who had had a throat culture that was positive for beta-hemolytic streptococci at that time (five from Georgia and two from Oklahoma). In addition, work areas, storage areas, unused disposable syringes, and the office laboratory were swabbed for bacteriologic culture. The alcohol soaked cotton ball container used in the Georgia outbreak had been cultured by the hospital laboratory prior to initiation of this investigation. All culture swabs were placed in 5 mL of Todd-Hewett broth for 24 hours before plating on sheep blood agar.

The vaccine remaining from the two multi-dose DTP vials that were used during the period of risk in the Oklahoma outbreak were cultured at the local hospital laboratory on October 21; all doses in the vial used during the period of risk in the Georgia outbreak had been given and the vial had been discarded. Twenty to forty unopened vials from the implicated vaccine lot in each outbreak were sent to the Office of Biologics, National Center for Biologics and Drugs, Food and Drug Administration, for sterility testing and measurement of level of thimerosal, the bacteriostatic preservative in the vaccine. The manufacturer of the implicated lot of DTP vaccine in the Georgia outbreak evaluated other unopened vials for bacterial content, thimerosal level, and ability to support growth of streptococci and staphylococci. Active surveillance for adverse events following use of DTP vaccine was initiated in regions of the United States where the implicated vaccine lot from each outbreak was being used.

Thirty-five additional vials of the implicated lot of DTP vaccine in the Georgia outbreak were obtained from a distribution center for challenge studies as the CDC. Serial twofold dilutions of a two-hour log growth phase culture of the strain of *Streptococcus* isolated from one child's abscess were prepared in Todd-Hewett broth and inoculated into vaccine vials (from 1,000 colony-forming units through 62.5 colony-forming units per vial). Three sets of two vials for each dilution were inoculated. Set 1 was incubated at 4 degrees C for the duration of the study. Set 2 was incubated at room temperature for four hours after inoculation and then incubated at 4 degrees C for the remainder of the study. Set 3 was incubated at 4 degrees C but warmed to room temperature for one hour prior to each sampling. Control vials for each set were inoculated with sterile Todd-Hewett broth. All vials were sampled at time zero, 4 hours, and 1, 2, 3, 7, 9, 15, 21, 28, 56, 84, and 112 days. Sampling was performed by thoroughly mixing vial contents and withdrawing 0.5 mL by syringe. This was mixed with 15 mL of melted trypticase soy agar to which 0.6 mL of defibrinated sheep blood was added. The contents (agar, blood, and vaccine) were mixed and poured into sterile Petri plates. Colony counts were read after 48 hours of incubation at 37 degrees C.

RESULTS

There were 12 children in the Georgia outbreak and seven children in the Oklahoma outbreak that met the case definition. Their symptoms and signs are presented in Table 1. Two of the children in the Georgia outbreak had a generalized rash, which clinically resembled scarlatina. Four of the children in the Georgia outbreak and five in the Oklahoma outbreak were hospitalized. All children had normal function in the affected limb at 1-month follow-up examinations.

TABLE 1. Symptoms and Signs in 19 Cases of Group A Streptococcal Abscesses

	Georgia (N = 12)	Oklahoma (N = 7)
Abscess	12	7
Fever <100.4 degrees C	12	7
Irritability	11	7
Vomiting	4	5
Scarlatina	2	0

In the Georgia pediatric practice, lot A of DTP vaccine had been used before and during the apparent risk period. On the afternoon of July 21, following the appearance of the first cases, the use of this lot was discontinued by the practice and use of lot B vaccine was begun. Of 14 children who received lot A vaccine between 2 and 4 PM on Monday, July 19, or between 9 AM and 12 noon on Tuesday, July 20, 12 (86%) children developed abscesses, compared with no abscesses among the 31 children vaccinated with the same lot of vaccine from 9 AM, July 15 to 12 noon, July 19 ($P < 10^{-9}$, Fisher's two-tailed exact test). Of the two children who received DTP vaccine during the high-risk period but did not develop abscesses, one developed a moderately severe local reaction that resolved spontaneously without therapy; the other had no reaction. Parents of 76 of 85 children (89%) who had received DTP vaccine from July 15 to July 22, but outside of the risk period, or other vaccines on July 19 and 20 reported no abscesses at injection sites or unusually severe or prolonged reactions. Parents of nine children were not available for interview; however, none of these children were immunized during the risk period. Only children who received DTP vaccine were at risk. None of the six children who received other immunizations during the risk period developed abscesses ($P = .0014$, Fisher's two-tailed exact test). Surveillance of other communities where 32,000 doses of lot A vaccine had been distributed uncovered no additional cases of abscesses.

In the Oklahoma pediatric practice, lot C of DTP vaccine (from a different manufacturer than vaccine associated with the Georgia outbreak) had been used before, during, and after the apparent risk period. Thirty-nine children had received vaccine injections in this practice from October 7 to 20. Parents of 38 of these children were interviewed. All seven children who met the case definition had received DTP consecutively on Friday, October 15, and Monday, October 18. None of the 16 children who received vaccines other than DTP met the case definition compared with seven of 22 children who received DTP ($P = .027$, Fisher's two-tailed exact test). One nurse stated that two vials of DTP may have been used during the apparent risk period. The first six children with abscesses had received their DTP from vial 1. Upon hearing that some children who had received DTP on October 15 were having severe local reactions, the nurses stopped using vial 1 about noon on October 18 and used vial 2 for the DTP immunization of the child who became the seventh case that afternoon. Surveillance of communities in Florida where this lot had been used uncovered no additional cases.

Group A *Streptococcus* was isolated from abscesses of nine of the 12 children in the Georgia outbreak and from abscesses of four of the seven children in the Oklahoma outbreak. Two of the hospitalized children in the Georgia outbreak also had blood cultures positive for group A *Streptococcus*. All 11 isolates from the Georgia outbreak were of the same type: T-28, M-nontypable, serum opacity reaction positive. All four isolates from the Oklahoma outbreak were also of a single type: T-3/13/B3264, M-nontypable, serum opacity reaction positive.

It was not possible to link a specific nurse with the administration of vaccine to any case in either outbreak. One nurse in each pediatric practice had a sore throat just prior to the onset of the outbreak. Group A *Streptococcus* was not isolated from any of the nurses, from any of the children with previously positive findings on throat cultures, or from any work areas or syringes in either pediatric practice.

Unopened vaccine vials from the vaccine lot in each outbreak were evaluated by the Office of Biologics and yielded no group A streptococcus; thimerosal was present within acceptable limits (0.0080% to 0.0120%, weight/volume). The vaccine remaining in vial 1 from the Oklahoma outbreak was cultured by the hospital laboratory three days following vaccination of the last child who developed abscesses (at least six of the seven children with abscesses received DTP from this vial) and grew group A *Streptococcus* of the same serotype as the abscesses; vial 2 was sterile.

A number of additional laboratory studies were done as part of the Georgia investigation. Culture of samples of lot A vaccine by the manufacturer yielded no group A *Streptococcus*. Preservative effectiveness tests done by the manufacturer using *Streptococcus pyogenes* (of a different strain from that isolated in this outbreak) indicated only 95.5% of the challenge organism was inactivated at 4 degrees C by 14 days after inoculation. In challenge studies at CDC, 29 of 30 vials from lot A vaccine yielded viable streptococci three days after inoculation. One of 30 vials yielded viable streptococci on day 15. No streptococci were isolated when vials were sampled after day 15.

The estimated medical costs of the Georgia outbreak are shown in Table 2. The total direct costs for the 12 cases was \$8,136 or \$678 per case. These costs do not include loss of work time by the parents of these children and do not include evaluation visits for children who received DTP on the high-risk days, but who were not ill.

TABLE 2. Estimated Direct Medical Costs of 12 Cases of Group A Streptococcal Abscess in Georgia

Hospitalization (actual for 4 children)	\$5,063
Surgical costs (actual for 12 children)	2,013
Pediatric re-visits (actual at \$20/visit)	620
Outpatient antibiotics (estimated at \$10/prescription)	120
Outpatient laboratory (estimated at \$40/child)	320
Total	\$8,136

DISCUSSION

These two outbreaks were probably each caused by contamination of a single multidose vial of DTP. First, all cases occurred in 12/14 and 7/7 children consecutively vaccinated with DTP vaccine. Second, all cultures yielded a single serotype in each outbreak, suggesting a common source. Other possible sources of infection are ruled out because no single nurse administered all of the vaccinations in either outbreak. Contamination of syringes or other materials used for vaccination is unlikely because no abscesses occurred in children who received other injections during the same high-risk period. In neither pediatric practice were there known changes in syringes, in other materials used for vaccination, or in vaccination technique between the high-risk period and the periods immediately preceding and following it.

The source of contamination could not be identified in either outbreak. In the Georgia outbreak, if the vial had been contaminated at the manufacturer, contamination would have had to occur in the fall of 1981 when the vaccine vials were filled. Because the vial in question was not used until July 1982, the streptococci would have had to survive for at least 8 months (or 5 months in the Oklahoma outbreak), an unlikely event in the presence of the demonstrated adequate levels of thimerosal. Challenge studies at the CDC using the organism from the Georgia cases, did not demonstrate any viable organisms 15 days or more after inoculation into unopened vials of DTP. It is more likely that the organisms were introduced after the vaccine vial was opened in both pediatric practices. The source of the streptococci may have been either from the personnel administering the immunizations or from patients with streptococcal infections that were cultured in the pediatric practices. Surface contamination of the vial's rubber stopper could have occurred after opening the stopper's cover and organisms could then have been introduced as the needle was inserted and air injected to withdraw the initial doses. Contamination of a single vial in each pediatric practice is supported by the failure, despite intensified surveillance, to detect outbreaks in other areas of the country where the lots from the two outbreaks were used and by the absence of cases associated with other vials used in these practices.

Pyogenic abscesses following receipt of DTP vaccine are rare. Only one other cluster, also caused by group A *Streptococcus*, has been reported to the CDC. That outbreak occurred in Indiana in February 1981 when seven children developed abscesses after vaccination with DTP vaccine. [n6] Investigation also implicated contamination of a single multidose vial from which a group A *Streptococcus*, T-1, M-1 strain was isolated. This outbreak in Indiana and the outbreaks in Georgia and Oklahoma are compared in Table 3.

TABLE 3. Three Recent Outbreaks of Group A Streptococcal Abscesses Following DTP Immunization

Cluster and Dates	No. of Abscesses	No. of Children with Positive Findings on Cultures	Streptococcus Type	Thimerosal Levels (wt/vol) n1
Indiana Feb 9-11, 1981	7	6	T-1, M-1	Not done
Georgia July 19 and 20, 1982	12	9	T-28, M nontypable	0.0092%
Oklahoma Oct 15 and 18, 1982	5	4	T-3/13/B3264, M nontypable	0.0088%

n1 Normal range = 0.0080% to 0.0120% (weight/volume).

The principal issue raised by these three outbreaks is how to prevent rare clusters of streptococcal or other pyogenic infections following use of multi-dose DTP vaccine vials. To avoid the occurrence of such events, the following options were considered: (1) increasing the concentration of the currently used preservative; (2) changing preservatives; (3) or switching to single-unit packaging.

The choice and level of preservative for inclusion in DTP vaccine is limited because of possible deleterious effects on the vaccine's antigenicity, and the need to assure safety of the preservative. Thimerosal, the preservative used in the production of DTP, is an organic mercurial bacteriostatic agent and is only weakly bactericidal. Laboratory experiments in this investigation have shown up to 2 weeks' survival of at least one strain of group A *Streptococcus* in multi-dose DTP vials. The manufacturer's preservative effectiveness tests showed that at 4 degrees C, 4.5% of the challenge *Streptococcus* survived 14 days after inoculation into a multi-dose DTP vaccine vial. At currently used concentrations, thimerosal is not an ideal preservative. However, because thimerosal is an organic mercurial compound, higher concentrations might reduce vaccine potency or pose a health hazard to recipients. No other preservatives that are currently available are as safe and effective as thimerosal.

Single-unit packaging would approximately double the cost of DTP per dose. For example, one manufacturer charges \$5.12 for a 15-dose vial of DTP vaccine or \$0.34, per dose. If the \$0.20 cost of a disposable syringe and needle are added, the total cost per dose to the physician would be about \$0.54. The same manufacturer charges \$10.40 for a package of ten single DTP doses (needle and syringe pre-packed) or \$1.04 per dose. Even though the actual incidence rate of such occurrences is not known, they are clearly quite rare. If we assume that there are as many as 100 cases per year, costing \$678 per abscess, the cost of these theoretical occurrences would be approximately \$68,000. Given the prices mentioned above and the fact that approximately 18 million doses of DTP are administered each year, the cost of switching to single-dose packaging might be approximately \$9 million. Neither research to develop a better preservative nor recommendations to consider single-dose packaging appear to be warranted as long as the occurrence of these outbreak remains rare.

To prevent future clusters of streptococcal or other pyogenic infections, it is important that all personnel administering DTP vaccine from multi-dose vials be aware of the potential for its contamination and resultant abscesses. The thimerosal preservative present in DTP vaccine requires substantial time to kill organisms and cannot be relied upon to prevent transmission of bacteria under conditions of practice when a vial is used over a short period. Instead, the most important means of preventing abscesses secondary to DTP vaccination is to prevent contamination by careful attention to sterile technique.

All personnel who learn of pyogenic abscesses following DTP immunization should report such occurrences to local health officials. Only then will the true extent of this problem be known.

SUPPLEMENTARY INFORMATION:

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REFERENCES:

- [n1.] Cody CL, Baraff LJ, Cherry JD, et al: Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981;68:650-660
- [n2.] Bernier RH, Frank JA, Nolan TF: Abscesses complicating DTP vaccination. Am J Dis Child 1981;135:826-828
- [n3.] Wilson GS: The Hazards of Immunization. London, Athlone Press, 1967
- [n4.] Madsen T, Henningsen EJ: Cases of streptococcal infection after injection for protection against diphtheria. Ugeskr Laeger 1929;101:203-206
- [n5.] Cayton HR, Morris CA: Injection site streptococcal abscesses in a clinic using disposable syringes. Mongr Bull Minist Health 1966;25:87-91
- [n6.] Greaves WL, Hinman AR, Facklam RR, et al: Streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination. Pediatr Infect Dis 1982;1:388-390