

Vapotherm Devices Contaminated With *Ralstonia*

BY MARY ANN MOON
Contributing Writer

Vapotherm respiratory gas administration devices are being voluntarily recalled, following federal government reports that 29 hospitals in 16 states found *Ralstonia* organisms colonizing the devices, and cultures from approximately 40 pediatric patients also yielded the bacteria.

The Centers for Disease Control and

Prevention and the Food and Drug Administration late last year had advised clinicians to use alternative devices to provide humidified oxygen therapy until the source of contamination has been identified and removed. They also recommended that any patients who have been exposed to the Vapotherm system be monitored for signs and symptoms suggesting infection, including fever, poor feeding, irritability, and changes in hematologic indices.

In addition, “clinicians may want to consider *Ralstonia* species infection in the differential diagnosis of symptomatic patients even if the organism has not been isolated,” the FDA said in a public health notification (www.fda.gov/cdrh/safety/122005-vapotherm.html).

In response, the device manufacturer, Vapotherm, announced last month that it would recall and disinfect Vapotherm 2000i and 2000h devices. Units will then be returned to the owners with updated dis-

infection and usage recommendations. Contamination of the Vapotherm system was first reported by the CDC and the FDA in October 2005, after a Pennsylvania hospital isolated *Ralstonia* in several patients who had used the device. The Vapotherm system is used “to add moisture to and to warm breathing gases for administration to patients,” according to its manufacturer, Vapotherm Inc. (Stevensville, Md.).

Since the October reports, the CDC and FDA have found additional cases of *Ralstonia* contamination. Cultures of unused Vapotherm cartridges at two hospitals yielded *Ralstonia*, but cultures of other unused cartridges from the same lot did not grow the organism.

After the procedures for disinfecting the device that were listed in its original instructions were found to be inadequate, the manufacturer issued new instructions for chloride dioxide disinfection.

However, this method also “may not achieve sustained bacterial control,” according to the FDA.

Several alternative devices are listed on the FDA Web site cited above.

Ralstonia, gram-negative bacteria usually found in water and soil and on plants, formerly were included in *Pseudomonas* or *Burkholderia* species and still can be misidentified as such. “Infections caused by *Ralstonia* should be treated on the basis of results of susceptibility testing of the patient’s isolate,” according to the CDC (MMWR 2005;54:1-2).

“Clinicians who elect to use Vapotherm are encouraged to weigh the risk of potential bacterial contamination of the device against the benefits Vapotherm might provide patients who require humidified oxygen therapy,” the CDC said.

For more information about the recall, visit www.vtherm.com/recall. Cases of colonization or infection with *Ralstonia* or related bacteria (gram-negative rods) in patients exposed to Vapotherm should be reported to the manufacturer, to local or state health departments, and to the CDC at 800-893-0485. Adverse events associated with medical devices should be reported to the FDA’s MedWatch program at www.fda.gov/Medwatch or by calling 800-332-1088 or faxing 800-332-0178.

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) ActHIB®

Caution: Federal (USA) law prohibits dispensing without prescription.

Brief Summary: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE ActHIB® or ActHIB® combined with AvP DTP vaccine by reconstitution is indicated for the active immunization of infants and children 2 through 18 months of age for the prevention of invasive disease caused by *H influenzae* type b and/or diphtheria, tetanus, and pertussis.

TriHIBit®, ActHIB® combined with Tripedia® by reconstitution, is indicated for the active immunization of children 15 to 18 months of age for prevention of invasive disease caused by *H influenzae* type b and diphtheria, tetanus, and pertussis. Antibody levels associated with protection may not be achieved earlier than 2 weeks following the last recommended dose.

Only AvP whole-cell DTP, Tripedia® or 0.4% Sodium Chloride diluent may be used for reconstitution of lyophilized ActHIB®, TriHIBit®, ActHIB® combined with Tripedia® by reconstitution, should not be administered to infants younger than 15 months of age.

As with any vaccine, vaccination with ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or 0.4% Sodium Chloride diluent may not protect 100% of susceptible individuals.

A single injection containing diphtheria, tetanus, pertussis, and Haemophilus b conjugate antigens may be more acceptable to parents and may increase compliance with vaccination programs. Therefore, in these situations it may be the judgment of the physician that it is of benefit to administer a single injection of whole-cell DTP or DTaP and Haemophilus b conjugate vaccines.

CONTRAINDICATIONS ActHIB® IS CONTRAINDICATED IN CHILDREN WITH A HISTORY OF HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE AND TO ANY COMPONENT OF DTP OR Tripedia® WHEN COMBINED BY RECONSTITUTION WITH THESE VACCINES. ANY CONTRAINDICATION FOR DTP IS A CONTRAINDICATION FOR ActHIB® RECONSTITUTED WITH DTP. ANY CONTRAINDICATION FOR Tripedia® IS A CONTRAINDICATION FOR TriHIBit®, (ActHIB® RECONSTITUTED WITH Tripedia®.) (Refer to product inserts for AvP whole-cell DTP and Tripedia®.)

WARNINGS If ActHIB® or ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia (TriHIBit®) is administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody responses may not be obtained. This includes patients with asymptomatic or symptomatic HIV-infection,¹ severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antineoplastic or radiation.² (Refer to product inserts for AvP whole-cell DTP and Tripedia®.)

TriHIBit®, ActHIB® combined with Tripedia® by reconstitution, should not be administered to infants younger than 15 months of age.

PRECAUTIONS GENERAL: Care is to be taken by the health-care provider for the safe and effective use of this vaccine. **EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ANAPHYLACTIC OR OTHER ALLERGIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.**

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, and to possible sensitivity to dry natural latex rubber, previous immunization history, current health status (see **CONTRAINDICATIONS, WARNINGS** sections), and a current knowledge of the literature concerning the use of the vaccine under consideration. (Refer to product inserts for AvP whole-cell DTP and Tripedia®.)

The health-care provider should ask the parent or guardian about the recent health status of the infant or child to be immunized including the infant's or child's previous immunization history prior to administration of ActHIB®, AvP DTP and Tripedia®.

Minor illnesses such as upper respiratory infection with or without low-grade fever are not contraindications for use of ActHIB®.³

As reported with Haemophilus b polysaccharide vaccines,⁴ cases of *H influenzae* type b disease may occur subsequent to vaccination and prior to the onset of protective effects of the vaccine.⁵ (See **INDICATIONS AND USAGE** section.) The evidence favors rejection of a causal relation between immunization with Hib conjugate vaccines and early-onset Hib disease.⁶

Antigenuria has been detected in some instances following receipt of ActHIB®; therefore, urine antigen detection may not have definitive diagnostic value in suspected *H influenzae* type b disease within 1 week of immunization.⁷

Special care should be taken to ensure that ActHIB® reconstituted with AvP DTP or Tripedia® or saline diluent (0.4% Sodium Chloride) is not injected into a blood vessel.

Administration of ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or saline diluent (0.4% Sodium Chloride) is not contraindicated in individuals with HIV infection.²

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be properly disposed.

Caution: The stopper of the diluent vial contains dry natural latex rubber which may cause allergic reactions. The lyophilized vaccine contains no rubber of any kind.

DRUG INTERACTIONS When AvP DTP is used to reconstitute ActHIB® or Tripedia® is used to reconstitute ActHIB® (TriHIBit®) and administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody response may not be obtained.

Immunosuppressive therapies, including irradiation, antineoplastic, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to defer vaccination until the patient has been off therapy for 1 month; otherwise, the patient should be vaccinated while still on therapy.³

If ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) has been administered to persons receiving immunosuppressive therapy, a recent injection of immunoglobulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

In clinical trials, ActHIB® was administered, at separate sites, concomitantly with 1 or more of the following vaccines: DTP, DTaP, Poliovirus Vaccine Live Oral (OPV), Measles, Mumps and Rubella vaccine (MMR), Hepatitis B vaccine and occasionally inactivated Poliovirus Vaccine (IPV). No impairment of the antibody response to the individual antigens, diphtheria, tetanus and pertussis, was demonstrated when ActHIB® was given at the same time, at separate sites, with IPV or MMR.⁵ In addition, more than 47,000 infants in Finland have received a third dose of ActHIB® concomitantly with MMR vaccine with no increase in serious or unexpected adverse events.⁵

No significant impairment of antibody response to Measles, Mumps and Rubella was noted in 15- to 20-month-old children who received TriHIBit®, ActHIB® reconstituted with Tripedia®, concomitantly with MMR. No data are available to the manufacturer concerning the effects on immune response of OPV, IPV or Hepatitis B vaccine when given concurrently with ActHIB® reconstituted with 0.4% Sodium Chloride, or AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®).⁵

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) has not been evaluated for its carcinogenic, mutagenic potential or impairment of fertility.

PREGNANCY REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or saline diluent (0.4% Sodium Chloride). It is also not known whether ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or saline diluent (0.4% Sodium Chloride) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or saline diluent (0.4% Sodium Chloride) is NOT recommended for use in a pregnant woman and is not approved for use in children 5 years of age or older.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF TriHIBit®, ActHIB® RECONSTITUTED WITH Tripedia®, IN INFANTS BELOW THE AGE OF 15 MONTHS HAVE NOT BEEN ESTABLISHED. (See **DOSAGE AND ADMINISTRATION** section.)

SAFETY AND EFFECTIVENESS OF ActHIB® RECONSTITUTED WITH AvP DTP OR SALINE DILUENT (0.4% SODIUM CHLORIDE) IN INFANTS BELOW THE AGE OF 6 WEEKS HAVE NOT BEEN ESTABLISHED. (See **DOSAGE AND ADMINISTRATION** section.)

ADVERSE REACTIONS More than 7,000 infants and young children (≤2 years of age) have received at least 1 dose of ActHIB® during US clinical trials. Of these, 1,064 subjects 12 to 24 months of age who received ActHIB® alone reported no serious or life threatening adverse reactions.

TABLE 1 ⁵ PERCENTAGE OF INFANTS PRESENTING WITH LOCAL REACTIONS AT 6, 24, AND 48 HOURS OF IMMUNIZATION WITH ActHIB® ADMINISTERED SIMULTANEOUSLY, AT SEPARATE SITES, WITH AvP DTP VACCINE												
REACTION	AGE AT IMMUNIZATION											
	2 Months (n=365)			4 Months (n=364)			6 Months (n=365)					
	6 Hrs	24 Hrs	48 Hrs	6 Hrs	24 Hrs	48 Hrs	6 Hrs	24 Hrs	48 Hrs	6 Hrs	24 Hrs	48 Hrs
Local*												
Tenderness	46.3%	11.5%	2.2%	23.4%	7.4%	1.1%	19.2%	6.0%	1.1%			
Erythema	14.3%	4.1%	0.3%	8.8%	5.8%	0.3%	11.5%	6.8%	1.6%			
Induration	22.5%	6.3%	1.9%	12.4%	4.7%	0.8%	9.8%	3.8%	1.1%			

*Local reactions were evaluated at the ActHIB® injection site.

Adverse reactions commonly associated with a first ActHIB® immunization of children 12 to 15 months of age who were previously unimmunized with any Haemophilus b conjugate vaccine, include local pain, redness, and swelling at the injection site. Systemic reactions include fever, irritability, and lethargy.^{5,8}

In a US trial, safety of TriHIBit®, ActHIB® combined with Tripedia® by reconstitution, in 110 children aged 15 to 20 months was compared to ActHIB® given with Tripedia® at separate sites to 110 children. All children received 3 doses of

Haemophilus b conjugate vaccine (ActHIB® or HibTITER®) and 3 doses of whole-cell DTP at approximately 2, 4, and 6 months of age.

TABLE 2 ⁵ PERCENTAGE OF 15- TO 20-MONTH-OLD CHILDREN PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS AT 6, 24, AND 48 HOURS OF IMMUNIZATION WITH TriHIBit® COMPARED TO ActHIB® AND TRIPEDIA® GIVEN CONCOMITANTLY AT SEPARATE SITES						
REACTION	6 Hrs Post-dose		24 Hrs Post-dose		48 Hrs Post-dose	
	Separate Injections*	TriHIBit®	Separate Injections*	TriHIBit®	Separate Injections*	TriHIBit®
Local						
Tenderness	n=110 17.3/20.0	n=110 13.1	n=110 8.2/8.2	n=110 10.0	n=110 1.8/0.9	n=110 1.8
Erythema >1"	0.9/0.0	3.6	2.7/0.9	3.6	0.9/0.0	1.8
Induration**	3.6/5.5	2.7	2.7/3.6	8.2	4.5/0.9	3.6
Swelling	3.6/3.6	3.6	2.7/1.8	5.5	0.9/0.0	4.5
Systemic						
Fever >102.2°F	n=103-110 0	n=102-109 2.0	n=105-110 1.0	n=103-108 1.9	n=104-110 1.9	n=103-109 0
Irritability	27.3	22.9	20.9	17.6	12.7	10.1
Drowsiness	36.4	30.3	17.3	13.9	12.7	11.0
Anorexia	12.7	9.2	10.0	6.5	6.4	2.8
Vomiting	0.9	1.8	0.9	1.9	0.9	2.8
Persistent cry	0	0	0	0	0	0
Unusual cry	0	0	0	0	0	0.9

*Tripedia® injection site/ActHIB® injection site.

**Induration is defined as hardness with or without swelling.

TriHIBit®, ActHIB® combined with Tripedia® by reconstitution, was administered to approximately 850 children, aged 15 to 20 months. All children received 3 doses of a Haemophilus b conjugate vaccine (ActHIB® or HibTITER®) and 3 doses of whole-cell DTP at approximately 2, 4, and 6 months of age. Local reactions were typically mild and usually resolved within the 24 to 48 hour period after immunization. The most common local reactions were pain and tenderness at the injection site. Systemic reactions occurring were usually mild and resolved within 72 hours of immunization. The reaction rates were similar to those observed in Table 2 when TriHIBit® (ActHIB® reconstituted with Tripedia®) was administered and when Tripedia® was administered alone as a booster.⁵

In a randomized, double-blind US clinical trial, ActHIB® was given concomitantly with DTP to more than 5,000 infants and Hepatitis B vaccine was given with DTP to a similar number. In this large study, deaths due to sudden infant death syndrome (SIDS) and other causes were observed but were not different in the 2 groups. In the first 48 hours following immunization, 2 definite and 3 possible seizures were observed after ActHIB® and DTP in comparison with none after Hepatitis B vaccine and DTP.⁵ This rate of seizures following ActHIB® and DTP was not greater than previously reported in infants receiving DTP alone. (Refer to product insert for AvP DTP.) Other adverse reactions reported with administration of other Haemophilus b conjugate vaccines include urticaria, seizures, hives, renal failure, and Guillain-Barre syndrome (GBS).^{5,9} A cause and effect relationship among any of these events and the vaccination has not been established.

When ActHIB® was given with DTP and inactivated poliovirus vaccine to more than 100,000 Finnish infants, the rate and extent of serious adverse reactions were not different from those seen when other Haemophilus b conjugate vaccines were evaluated in Finland (ie, HibTITER®, ProHIBit®).⁵

However, the number of subjects studied with TriHIBit®, ActHIB® combined with Tripedia® by reconstitution, was inadequate to detect rare serious adverse events.

DOSAGE AND ADMINISTRATION Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

RECONSTITUTION: Using Aventis Pasteur Inc. DTP, cleanse both the DTP and ActHIB® vial rubber stoppers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of AvP DTP then withdraw a 0.6 mL dose and inject into the vial of lyophilized ActHIB®. After reconstitution and thorough agitation, the combined vaccines will appear whitish in color. Withdraw and administer 0.5 mL dose of the combined vaccines intramuscularly. Vaccine should be used within 24 hours after reconstitution.

To prepare TriHIBit®, cleanse both the Tripedia® and ActHIB® vial rubber stoppers with a suitable germicide prior to reconstitution. Thoroughly agitate the vial of AvP Tripedia® then withdraw a 0.6 mL dose and inject into the vial of lyophilized ActHIB®. After reconstitution and thorough agitation, the combined vaccines will appear whitish in color. Withdraw and administer 0.5 mL dose of the combined vaccines intramuscularly. Vaccine should be used immediately (within 30 minutes) after reconstitution.

Using saline diluent (0.4% Sodium Chloride) cleanse the vaccine vial rubber stopper with a suitable germicide and inject the entire volume of diluent contained in the vial or syringe into the vial of lyophilized vaccine. Thorough agitation is advised to ensure complete reconstitution. The entire volume of reconstituted vaccine is then drawn back into the syringe before injecting one 0.5 mL dose intramuscularly. The vaccine will appear clear and colorless. Vaccine should be used within 24 hours after reconstitution.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

DO NOT INJECT INTRAVENOUSLY.

Each dose of ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or saline diluent (0.4% Sodium Chloride) is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

When ActHIB® is reconstituted with AvP DTP, the combined vaccines are indicated for infants and children 2 through 18 months of age for intramuscular administration in accordance with the schedule indicated in Table 3.⁵ When ActHIB® is reconstituted with Tripedia® (TriHIBit®), the combined vaccines are indicated for children 15 to 18 months of age for intramuscular administration in accordance with the schedule in Table 3.⁵

TABLE 3 ⁵ RECOMMENDED IMMUNIZATION SCHEDULE FOR ActHIB® AND DTP OR TRIPEDIA® For Previously Unvaccinated Children		
DOSE	AGE	IMMUNIZATION
First, Second, and Third	At 2, 4, and 6 months	ActHIB® reconstituted with DTP or with saline diluent (0.4% Sodium Chloride)
Fourth	At 15 to 18 months	ActHIB® reconstituted with DTP or Tripedia® (TriHIBit®) or with saline diluent (0.4% Sodium Chloride)
Fifth	At 4 to 6 years	DTP or Tripedia®

For Previously Unvaccinated Children

The number of doses of Haemophilus b Conjugate Vaccine indicated depends on the age at which immunization is begun. A child 7 to 11 months of age should receive 2 doses of Haemophilus b Conjugate Vaccine at 8-week intervals and a booster dose at 15 to 18 months of age. A child 12 to 14 months of age should receive 1 dose of Haemophilus b Conjugate Vaccine followed by a booster 2 months later.

Preterm infants should be vaccinated according to their chronological age from birth.¹⁰

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with ActHIB® reconstituted with AvP DTP or ActHIB® reconstituted with Tripedia® (TriHIBit®) or saline diluent (0.4% Sodium Chloride). There is no need to start the series over again, regardless of the time elapsed between doses.

It is acceptable to administer a booster dose of TriHIBit® (ActHIB® reconstituted with Tripedia®) following a primary series of Haemophilus b conjugate and whole-cell DTP vaccines, or a primary series of a combination vaccine containing whole-cell DTP.

STORAGE Store lyophilized vaccine packaged with saline diluent, Diphtheria and Tetanus Toxoids and Pertussis or Tripedia® between 2–8°C (35–46°F). **DO NOT FREEZE.**

Journal Advertising References From Previous Page:

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