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Pertussis Vaccination: Acellular Pertussis Vaccines for Reinforcing and Booster Use-Supplementary ACIP Statement

Recommendations of the Immunization Practices Advisory Committee (ACIP) of the U.S. Public Health Service*

This supplementary statement provides information on and recommendations for the use of diphtheria and tetanus toxoids and acellular pertussis vaccines (DTaP). Two such vaccines were recently licensed, ACEL-IMUNE®,§ and Tripedia.™ ¶ Tripedia™ has a formulation that differs from that of ACEL-IMUNE®. Both DTaP vaccines are licensed for use only as the fourth and/or fifth doses of diphtheria, tetanus, and pertussis vaccination; they are not licensed for the initial three-dose series for infants and children, regardless of age. Whole-cell DTP should continue to be used for the initial three-dose series and remains an acceptable alternative for the fourth and fifth doses. The current Immunization Practices Advisory Committee (ACIP) statement on diphtheria, tetanus, and pertussis, summarized in last month's Bulletin, *gives general recommendations on pertussis prevention, including the use of whole-cell pertussis vaccines for primary and booster vaccination.*

Introduction

Current Whole-Cell Pertussis Vaccines

Simultaneous vaccination against diphtheria, tetanus, and pertussis during infancy and childhood has been a recommended routine practice in the United States since the late 1940s. Whole-cell pertussis vaccines in the United States have been and continue to be prepared from suspensions of killed *Bordetella pertussis* whole bacterial cells. Routine vaccination with whole-cell vaccines has been highly effective in reducing the burden of disease and deaths due to pertussis. Whole-cell pertussis vaccines, although safe, are associated with a variety of expected adverse events; these concerns have led to attempts to develop safer pertussis vaccines that have high efficacy.

In This Issue:

Acellular Pertussis Vaccines

Several antigenic components of *Bordetella pertussis* have been identified. Candidate acellular pertussis vaccines, produced by multinational manufacturers, are now available due to advances in the methods of purifying and preparing these components. In general, these vaccines are immunogenic and are less likely to cause common adverse reactions than the current whole-cell preparations. Several clinical trials, which compare relative protective efficacy of primary vaccination utilizing diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines with that of whole-cell vaccines administered to infants, are in progress or development. A lack of adequate evidence, until recently, to demonstrate the effectiveness of any single preparation has delayed U.S. licensure for any indication of a candidate acellular pertussis vaccine. In the past year, the Food and Drug Administration (FDA) licensed the DTaP vaccines ACEL-IMUNE® and Tripedia™ for use as the fourth and/or fifth doses of the recommended DTP series.

ACEL-IMUNE® Information. ACEL-IMUNE® contains 40 mcg of protein; approximately 86% of this protein is filamentous hemagglutinin (FHA); 8%, pertussis toxin (PT); 4%, pertactin (Pn); and 2%, fimbriae (Fim) type 2. The acellular pertussis vaccine component is purified by ammonium sulfate fractionation and sucrose density gradient centrifugation; PT is detoxified by treatment with formaldehyde. Each dose of ACEL-IMUNE® contains 1.5 limit of flocculation (Lf) of diphtheria toxoid, 5.0 Lf of tetanus toxoid, and 300 hemagglutinating (HA) units of acellular pertussis vaccine. The FHA and PT

components both exhibit HA activity. The combined components are adsorbed to aluminum hydroxide and aluminum phosphate and preserved with 1:10,000 thimerosal.

Tripedia™ Information. Tripedia™ vaccine components are purified from *Bordetella pertussis* by salt precipitation, ultracentrifugation, and ultrafiltration. After purification, FHA and PT are combined to obtain a 1:1 ratio and are then treated with formaldehyde to inactivate PT. Each dose of Tripedia™ contains 23.4 mcg protein of FHA and 23.4 mcg protein of inactivated PT (toxoid), as well as 6.7 Lf of diphtheria toxoid and 5.0 Lf of tetanus toxoid. The combined components are adsorbed to aluminum potassium sulfate and preserved with 1:10,000 thimerosal.

The following evidence supports the use of ACEL-IMUNE® or Tripedia™ after the initial infant three-dose series of whole-cell DTP vaccine.

Immunogenicity. When ACEL-IMUNE® is used for the fourth and fifth doses of the vaccination series, antibody responses after administration are generally similar to those following whole-cell DTP vaccine for the PT, Pn, and Fim components; antibody responses are higher for FHA.

Antibody responses to PT and FHA following administration of Tripedia™ as the fourth and fifth doses of the vaccination series are similar to or higher than those following whole-cell DTP vaccine. Data are available to demonstrate the immunogenicity of Tripedia™ among children ages 15-16 months.

Clinical efficacy. In Japan, Takeda-manufactured DTaP vaccine has been shown to prevent pertussis disease among children age ≥2 years, however, in this retrospective study clinicians and investigators were not blinded to the vaccination status of the participants. The occurrence of pertussis was compared in 62 children vaccinated with two to four doses of Takeda DTaP on or after the second birthday and 62 unvaccinated children for the period 7-30 days after household exposure to pertussis. Typical clinical pertussis occurred in one vaccinated child and 43 unvaccinated children; estimated clinical vaccine efficacy: 98% (95% CI, 84%-99%). Minor respiratory illness, possibly representing mild, atypical pertussis, occurred among an additional eight vaccinated and four unvaccinated children. When these children were included, the estimated vaccine efficacy was 81% (95% CI, 64%-90%). None of the vaccinated household contacts in this study were age <2 years; by restricting the analysis of results to household contacts who were age ≥2 years, the corresponding estimates of efficacy were 97% (95% CI, 82%-99%) and 79% (95% CI, 60%- 89%) respectively. In a smaller study of similar design, results were similar.

The efficacy of two acellular pertussis vaccines developed by the Japan National Institute of Health (JNIH) and prepared by BIKEN was studied in 1985-1987 in a randomized, placebo-controlled clinical trial in Sweden. One of the vaccines (JNIH-6) contained 23.4 mcg protein/dose each of formaldehyde-treated PT and FHA. The first dose of vaccine or placebo was administered at 5-11 months of age; the second dose was administered 8-12 weeks later. For culture-confirmed disease with cough of any duration, the observed efficacy for JNIH-6 was 69% (95% confidence interval [CI], 47%-82%); for culture-confirmed pertussis with cough lasting >30 days, the observed efficacy was 79% (95% CI, 57%-90%). Non-blinded follow-up studies conducted over a 42-month interval after the trial had ended support the efficacy estimates obtained from the clinical trial.

The experiences in Sweden and Japan, however, do not satisfactorily define whether acellular pertussis vaccines confer clinical protection when administered early in infancy (i.e., 2, 4, and 6 months of age) and whether protection induced at any age is equivalent to that of whole-cell pertussis vaccine preparations.

Table 1. Routine Diphtheria, Tetanus, and Pertussis Vaccination Schedule Summary for Children <7 Years of Age

Dose	Age	Customary age/interval	Product
Primary 1	2 months	≥6 weeks of age	DTP*
Primary 2	4 months	4–8 weeks after first dose†	DTP*
Primary 3	6 months	4–8 weeks after second dose†	DTP*
Primary 4	15 months	6–12 months after third dose†	DTaP or DTP*§
Booster	Age 4–6 years, before entering kindergarten or elementary school (not necessary if fourth primary vaccinating dose administered after fourth birthday)		DTaP or DTP*§
Additional boosters	Every 10 years after last dose		Td¶

*Use DT if pertussis vaccine is contraindicated. If the child is age ≥1 year at the time that primary dose three is due, a third dose 6–12 months after the second dose is administered completes primary vaccination with DT.
†Prolonging the interval does not require restarting series.
§Either DTaP or whole-cell DTP can be used for the fourth and fifth doses; DTaP is generally preferred, if available.
¶Tetanus-diphtheria toxoids absorbed (Td) (for adult use).

Safety. Local reactions, fever, and other common systemic events occur less frequently after receipt of acellular pertussis vaccinations than after whole-cell DTP vaccination. In general, local and common systemic events occur approximately one-fifth to two-thirds the frequency after whole-cell DTP vaccination.

Vaccine usage

See the general ACIP statement on diphtheria, tetanus, and pertussis (in last month's issue) for more details.

DTaP preparations are currently licensed only for use as the fourth and/or fifth doses of the DTP series among children ages 15 months through 6 years (before the seventh birthday). Any of the licensed whole-cell DTP or DTaP preparations can be used interchangeably for the fourth and fifth doses of the routine series of vaccination against diphtheria, tetanus, and pertussis among children ≥15 months of age. The ACIP Committee recommends the use of DTaP, if readily available, because it substantially reduces local reactions, fever, and other common systemic events that often follow receipt of whole-cell DTP. There are no specific data to support the use of one particular DTaP vaccine product over the other. No data exist regarding the intermixed use of the two DTaP products at the fourth and fifth doses of the series with respect to safety, immunogenicity, or efficacy.

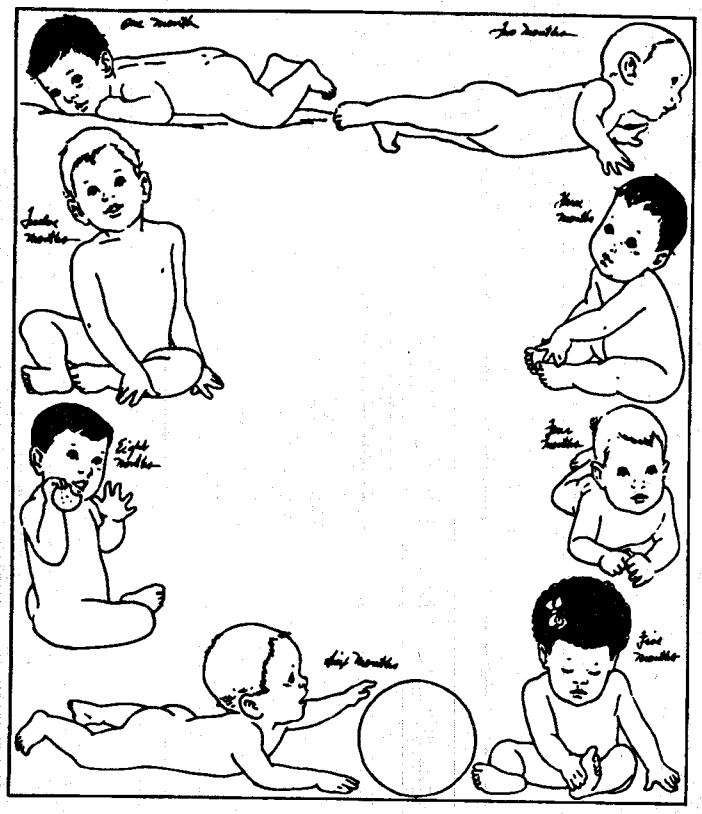
Either vaccine can be administered to children as part of the recommended schedule of routine simultaneous vaccination with DTP; oral poliovirus vaccine (OPV); measles, mumps, and rubella vaccine (MMR); and, when appropriate, *Haemophilus* b conjugate vaccine (HbCV) at 15-18 months of age.

Use of DTaP is not recommended for children who have received less than three doses of whole-cell DTP, regardless of age. The Committee considers the first four DTP doses as primary immunization against diphtheria, tetanus, and pertussis. The fourth (reinforcing) dose of DTP, generally given at age 15-18 months, is administered to maintain adequate pertussis immunity during the preschool years. The fifth (booster) dose of DTP is administered at ages 4-6 years of age to confer continued protection against exposure during the early years of school.

The standard, single-dose volume of either vaccine (ACEL-IMUNE® or Tripedia™) is 0.5 mL and should be administered intramuscularly (IM).

Indications for the Fourth (Reinforcing) Dose

Six to 12 months after the third dose of DTP. One dose of DTaP (instead of whole-cell DTP) can be administered IM to children age 15-18 months (or later when necessary); this dose should be administered at least 6 months after the third dose of whole-cell DTP (Table 1). The fourth dose of either DTaP or DTP is an integral part of the primary immunizing course of pertussis vaccination. DTaP is not licensed for use among children age <15 months. Although immunogenicity data among children age 15-16 months are not yet available, the Committee suggests that acellular pertussis vaccines be used for children as part of the recommended schedule of routine simultaneous vaccination with DTP, oral poliovirus (OPV), and measles-mumps-rubella (MMR) at age 15-18 months.



Booster Vaccination

Children 4-6 years of age (up to the seventh birthday). A dose of DTaP can be administered as the fifth dose in the series for children ages 4-6 years who either have received all four prior doses as whole-cell vaccine or for those children who have received three doses of whole-cell DTP and one dose of DTaP. A fifth dose of either DTaP or DTP should be administered before the child enters kindergarten or elementary school. The Committee recommends the use of DTaP, if readily available. This fifth dose is not necessary if the fourth dose in the series is given on or after the fourth birthday.

Special Considerations

Vaccination of infants and young children who have a personal or family history of seizures. Recent data suggest that infants and young children who have had previous seizures (whether febrile or nonfebrile) or who have immediate family members with such histories are at higher risk of seizures following DTP vaccination than those without such histories. Because these reactions may be due to the fever induced by whole-cell DTP vaccine and because DTaP is infrequently associated with moderate to high fever, use of DTaP is strongly recommended for the fourth and fifth doses if pertussis vaccination is considered for these children (see Precautions and Contraindications). A family history of seizures or other central nervous disorders does not justify withholding pertussis vaccination. Acetaminophen should be given at the time of DTP or DTaP vaccination and every 4 hours for 24 hours to reduce the possibility of postvaccination fever in these children.

Children with a contraindication to pertussis vaccination (see Precautions and Contraindications). For children younger than age 7 years who have a contraindication to whole-cell pertussis vaccine, DT should be used instead of DTP; DTaP should not be substituted. If additional doses of pertussis vaccine become contraindicated after a DTP series is begun in the first year of life, DT should be substituted for each remaining scheduled DTP dose.

Pertussis vaccination for persons age ≥7 years. Adolescents and adults who have waning immunity are a major reservoir for transmission of pertussis. It is possible that a booster dose of another preparation of acellular pertussis vaccine will be recommended in the future for persons age ≥7 years, although it is not currently recommended.

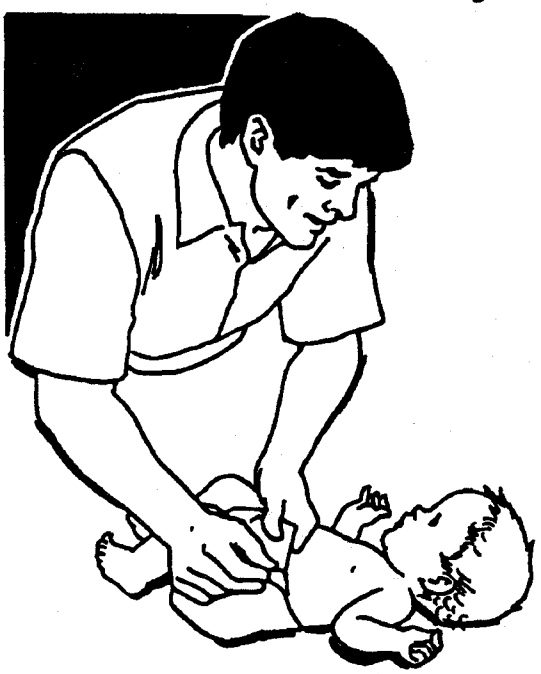
Side effects and adverse reactions

For a complete discussion, see the general ACIP statement on diphtheria, tetanus, and pertussis in last month's issue.

Although mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia occur frequently after both whole-cell DTP vaccination and DTaP vaccination, they are less common after DTaP vaccination. These reactions are self-limited and can be safely managed with symptomatic treatment.

Moderate-to-severe systemic events, including fever ≥40.5 C (105 F); persistent, inconsolable crying lasting 3 hours or more; and collapse (hypotonic-hyporesponsive episode) have been rarely reported after vaccination with DTaP. Each of these events appears to occur less often than with whole-cell DTP. When these events occur after the administration of whole-cell DTP, they appear to be without sequelae; the limited experience with DTaP suggests a similar outcome.

In U.S. studies, more severe neurologic events, such as prolonged convulsions or encephalopathy, have not been reported in temporal association after administration of over 6,000 doses of ACEL-IMUNE® and over 11,000 doses of Tripedia™, respectively. This somewhat limited experience does not allow conclusions to be drawn whether any rare serious adverse events will occur after administration of DTaP. Because DTaP causes fever less frequently than whole-cell DTP, it is anticipated that events such as febrile convulsions will be less common after receipt of DTaP.



Simultaneous administration of vaccines

The simultaneous administration of DTaP, OPV, and MMR has not been evaluated. However, on the basis of studies using whole-cell DTP, the Committee does not anticipate any differences in seroconversion rates and rates of side effects from those observed when the vaccines are administered separately. Although combinations have not been thoroughly studied, simultaneous vaccination with DTaP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and *Haemophilus* b conjugate vaccine (HbCV) is acceptable; similarly, simultaneous vaccination with DTaP, hepatitis B vaccine (HBV), OPV, IPV, and HbCV is also acceptable. The Committee recommends the simultaneous administration of all vaccines appropriate to the age and the previous vaccination status of the child, including the special circumstance of simultaneous administration of DTP or DTaP, OPV, HbCV, and MMR at age ≥15 months.

Precautions and contraindications

DTaP is licensed only for reinforcing and booster immunization, i.e., the fourth and fifth doses in the DTP series. DTaP is not licensed for use among children age <15 months, on or after the seventh birthday, or for the initial three-dose series among infants and children regardless of their age.

Contraindications

Because no data currently exist to suggest otherwise, contraindications to further doses of DTaP are the same as those for the whole-cell DTP. If any of the following events occurs in temporal relation with the administration of DTP or DTaP, subsequent vaccination with DTP or DTaP is contraindicated:

1. An immediate anaphylactic reaction.
2. Encephalopathy (not due to another identifiable cause), defined as an acute, severe central nervous system disorder occurring within 7 days after vaccination and generally consisting of major alterations in consciousness, unresponsiveness, or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours.

Precautions (Warnings)

If any of the following events occurs in temporal relation with the receipt of either whole-cell DTP or DTaP, the decision to administer subsequent doses of vaccine containing the pertussis component should be carefully considered. Although these events were once considered absolute contraindications to whole-cell DTP, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh the possible risks, particularly since the following events have not been proven to cause permanent sequelae:

1. Temperature of ≥40.5 C (105 F) within 48 hours, not due to another identifiable cause.
2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
3. Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours.
4. Convulsions with or without fever, occurring within 3 days.

If these events occur after receipt of any of the first four doses of whole-cell DTP vaccine and if additional doses of pertussis vaccine are indicated because the potential benefits outweigh the potential risks, consideration should be given to the use of DTaP for the fourth and fifth doses.

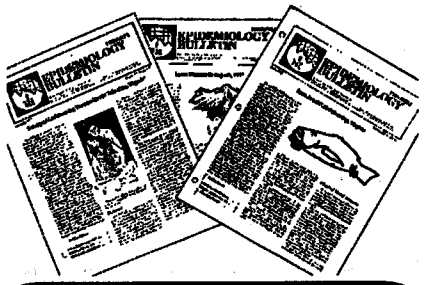
Reporting of adverse events after vaccination

As with any newly licensed vaccine, surveillance for information regarding the safety of DTaP in large-scale use is important. Surveillance information aids in the assessment of vaccine safety, although its usefulness is limited, by identifying potential events that may warrant further study. Additionally, specific evaluations of DTaP use in larger populations than those studied for license application are being initiated.

The Vaccine Adverse Event Reporting System (VAERS) of the Department of Health and Human Services became operational in November, 1990. VAERS is designed to accept reports of all serious adverse events that occur after receipt of DTaP, as well as any other vaccine, including but not limited to those mandated by the National Childhood Vaccine Injury Act of 1986. Any questions about reporting requirements, completion of the report form, or requests for reporting forms can be directed to 1-800-822-7967.

**Adapted from MMWR 1992;41(No. RR-1):1-10, and MMWR 1992;41(No. RR-15):1-5.*

§Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed is prepared and distributed as ACEL-IMUNE® by Lederle Laboratories (Pearl River, New



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York) and was licensed December 17, 1991 (2). The acellular pertussis vaccine component is produced by Takeda Chemical Industries, Ltd. (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Lederle Laboratories.

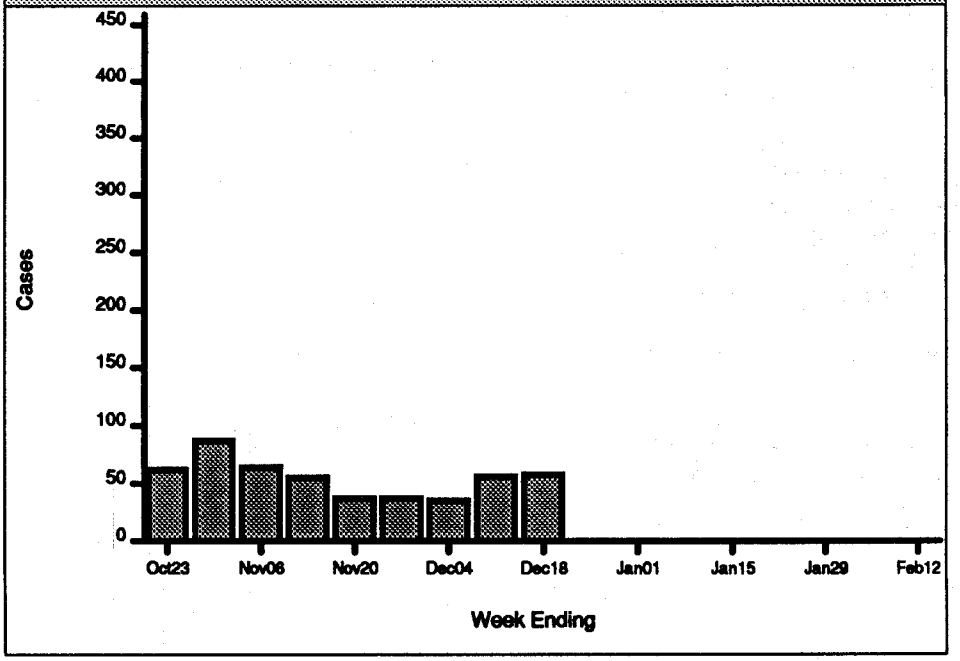
¶Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, prepared and distributed as Tripedia™ by Connaught Laboratories, Inc. (Swiftwater, Pennsylvania), was licensed August 21, 1992. The purified acellular pertussis vaccine component is produced by BIKEN/Tanabe Corporation (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Connaught Laboratories.

Crackdown on Raccoon Trade

State and federal wildlife agents have completed a 2-year investigation of the illegal sale of raccoons to hunting clubs in Virginia. Importation of raccoons into Virginia has been banned since the early 1980s; however, significant black market trade continues. A cooperative investigation conducted by U.S. Fish and Wildlife Service agents and personnel with the Virginia Department of Game and Inland Fisheries culminated with the indictment of three individuals by a Federal Grand Jury in Abingdon, Virginia, in February 1992. Dr. Victor Nettles of the Southeastern Cooperative Wildlife Disease Study (College of Veterinary medicine, The University of Georgia) testified before the Grand Jury to stress the serious human, livestock, and wildlife health implications associated with raccoon relocation. Major health concerns are rabies virus and the neurotropic intestinal roundworm *Baylisascaris procyonis*. The Grand Jury validated charges of conspiracy and numerous counts of shipping raccoons from Ohio to Virginia in violation of the Lacey Act. Resultant fines exceeded $30,000, and one individual received a 60-day jail sentence. Evidence provided by law enforcement agents documented the shipment of approximately 2,845 raccoons from Ohio to Virginia during the past 5 years. The sale price of these animals was estimated at $56,900. Hopefully, awareness of this legal action and publicity of the serious animal and human health dangers associated with translocating raccoons will serve as deterrents to future raccoon trafficking.

Reprinted from: Southeastern Cooperative Wildlife Disease Study. SCWDS Briefs. 1992;8(3).

Reports of Influenza-like Illness from Sentinel Physicians (34 Offices Reporting) in Virginia Through December 18. Activity in December was Characterized as Sporadic with no Laboratory Isolates Reported in Virginia. Nationally, Washington State has Reported a Culture-confirmed Outbreak of Influenza B.



Cases of Selected Notifiable Diseases, Virginia, November 1 through November 30, 1992.

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
		Regions							
	State	NW	N	SW	C	E	This Yr	Last Yr	5 Yr Avg
AIDS	53	3	22	9	5	14	645	625	425
Campylobacter	43	10	15	3	9	6	590	602	604
Gonorrhea*	481	-	-	-	-	-	14048	16938	14947
Hepatitis A	39	2	17	10	6	4	140	179	267
Hepatitis B	16	1	6	2	0	7	174	202	289
Hepatitis NANB	5	0	0	3	0	2	35	30	51
Influenza	1	0	0	0	0	1	131	791	1471
Kawasaki Syndrome	1	0	0	0	0	1	21	24	22
Legionellosis	1	0	0	0	0	1	19	16	13
Lyme Disease	9	0	3	0	4	2	109	143	73
Measles	1	0	0	1	0	0	16	30	72
Meningitis, Aseptic	43	2	11	4	1	25	275	407	318
Meningitis, Bacterial~	5	1	1	1	0	2	103	122	150
Meningococcal Infections	5	0	2	1	0	2	55	33	54
Mumps	3	0	1	0	0	2	52	61	100
Pertussis	5	1	0	3	1	0	15	24	31
Rabies in Animals	30	14	10	1	2	3	337	240	270
Reye Syndrome	0	0	0	0	0	0	0	2	1
Rocky Mountain Spotted Fever	2	0	1	1	0	0	23	20	20
Rubella	0	0	0	0	0	0	0	0	3
Salmonellosis	73	13	20	7	19	14	866	1241	1459
Shigellosis	18	3	6	0	6	3	216	368	310
Syphilis (1° & 2°)*	50	0	2	9	4	35	671	843	611
Tuberculosis	8	0	0	2	2	4	312	289	348

Localities Reporting Animal Rabies: Alexandria 1 raccoon; Arlington 1 raccoon; Augusta 1 cow, 2 skunks; Charles City 1 raccoon; Chesterfield 1 bat; Culpeper 1 skunk; Fairfax 4 raccoons, 1 skunk; Fauquier 1 raccoon; Franklin County 1 raccoon; Frederick 1 raccoon; James City 1 raccoon; Loudoun 1 fox, 2 raccoons; Page 3 skunks; Rockingham 2 skunks; Shenandoah 1 cow, 1 skunk; Suffolk 2 raccoons; Warren 1 raccoon.
Occupational Illnesses: Asbestosis 6; Byssinosis 1; Carpal Tunnel Syndrome 57; Coal Worker's Pneumoconiosis 12; Loss of Hearing 9; Malignant Mesothelioma 1; Repetitive Motion Disorder 3.

*Total now includes military cases to make the data consistent with reports of the other diseases.
~Other than meningococcal

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