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VACCINE QUARTERLY

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ABBREVIATIONS

AAFP	American Academy of Family Physicians	IPV	inactivated polio vaccine
AAP	American Academy of Pediatrics	LAIV	(trivalent) live attenuated influenza vaccine
ACIP	Advisory Committee on Immunization Practices	MMR	measles, mumps, and rubella vaccine
CDC	Centers for Disease Control and Prevention	PCR	polymerase chain reaction
CI	confidence interval	Td	tetanus and diphtheria vaccine
DTaP	diphtheria, tetanus, and acellular pertussis vaccine	Tdap	tetanus, diphtheria, and acellular pertussis vaccine
HepB	Hepatitis B vaccine	TIV	trivalent (inactivated) influenza vaccine
Hib	<i>Haemophilus influenzae</i> type b vaccine	VFC	Vaccines for Children
HIV	human immunodeficiency virus	VSD	Vaccine Safety Datalink

LICENSED VACCINES

ActHIB®	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate); sanofi pasteur Inc., Swiftwater, PA	PEDIARIX®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined; GlaxoSmithKline Biologicals, Rixensart, Belgium
ADACEL®	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed; sanofi pasteur Inc., Swiftwater, PA	PedvaxHIB®	Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate); Merck & Co., Inc., West Point, PA
BOOSTRIX®	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed; GlaxoSmithKline Biologicals, Rixensart, Belgium	PENTACEL®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined; sanofi pasteur Inc., Swiftwater, PA
DAPTACEL®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed; sanofi pasteur Inc., Swiftwater, PA	POLIOVAX®	Poliovirus Vaccine Inactivated (Human Diploid Cell); sanofi pasteur Inc., Swiftwater, PA
INFANRIX®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed; GlaxoSmithKline Biologicals, Rixensart, Belgium	ROTARIX®	Rotavirus Vaccine, live attenuated; GlaxoSmithKline Biologicals, Rixensart, Belgium
KINRIX™	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine; GlaxoSmithKline Biologicals, Rixensart, Belgium	RotaTeq®	Rotavirus Vaccine, Live, Oral, Pentavalent; Merck & Co., Inc., Whitehouse Station, NJ
		VARIVAX®	Varicella Virus Vaccine Live (Oka/Merck); Merck & Co., Inc., Whitehouse Station, NJ
		ZOSTAVAX®	Zoster Vaccine Live (Oka/Merck); Merck & Co., Inc., Whitehouse Station, NJ

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Faculty Credentials and Financial Disclosure Information

Gary S. Marshall, MD is Professor of Pediatrics and Chief of the Division of Pediatric Infectious Diseases at the University of Louisville School of Medicine in Louisville, Kentucky.

(Dr. Marshall was/is the recipient of research grants from, and was/is a member of the speakers' bureaus of, GlaxoSmithKline, Merck & Co., Inc., and sanofi pasteur Inc.; and was/is a consultant for GlaxoSmithKline, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, and sanofi pasteur Inc.)

James H. Conway, MD is Associate Professor of Pediatrics at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin.

(Dr. Conway was/is the recipient of research grants from Merck Foundation; was/is a consultant for Merck Pediatric Vaccines; and was/is a member of the speakers' bureaus of GlaxoSmithKline, MedImmune, Inc., and sanofi pasteur Inc.)

Sharon G. Humiston, MD, MPH is Associate Professor of Emergency Medicine and Pediatrics at the University of Rochester School of Medicine and Dentistry in Rochester, New York.

(Dr. Humiston was/is a consultant for, and was/is a member of the speakers' bureaus of, GlaxoSmithKline, Merck & Co., Inc., and sanofi pasteur Inc.; and is a consultant for, and is a member of the speakers' bureau of, Novartis Pharmaceuticals Corporation.)

Jay M. Lieberman, MD is Professor of Clinical Pediatrics at the University of California, Irvine, and Medical Director for Infectious Diseases at Quest Diagnostics/Focus Diagnostics in Cypress, California.

(Dr. Lieberman was a member of the speaker's bureau of Merck & Co., Inc.; and is an employee of Quest Diagnostics/Focus Diagnostics.)

Charles R. Woods, MD, MS is Professor of Pediatrics in the Department of Pediatrics at the University of Louisville School of Medicine, Louisville, Kentucky.

(Dr. Woods was/is the recipient of research grants from sanofi pasteur Inc. and Wyeth Pharmaceuticals Inc.; and was/is a member of the speakers' bureaus of MedImmune, Inc., Merck & Co., Inc., Pfizer Inc., and sanofi pasteur Inc.)

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The authors have no financial interest or other relationship with the makers of commercial products discussed in this publication unless so indicated.

Advocating for Safe and Effective Vaccines

Diane C. Peterson, BS

**Associate Director for Immunization Projects
Immunization Action Coalition
St. Paul, Minnesota**

(Ms. Peterson has disclosed that she has no significant relationships with, or financial interests in, any commercial companies pertaining to this educational activity.)

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Learning Objectives: After reading this article, physicians should be able to identify resources that are available to help them stay informed about current vaccine issues; and to become stronger advocates for the continued availability of safe and effective vaccines.

Introduction

In the early 1900s, deaths from smallpox and diphtheria were commonplace in the U.S.^{1,2} The last indigenous case of smallpox in the U.S. occurred in 1949, and by 1977 smallpox had been eradicated from the face of the earth.³ Cases of diphtheria are virtually unheard of. The last case of wild-type poliomyelitis in the Western Hemisphere occurred in 1991, and the disease is now confined to just 5 countries in the world.⁴ By the end of the 20th century, endemic transmission of measles and rubella in the U.S. had ceased.^{5,6} It is no wonder that vaccines have been hailed as one of the 10 most important achievements in public health⁷ (see *The Vaccine Quarterly* 2008;2[2]:12–13).

With these successes, however, has come widespread complacency about the seriousness of vaccine-preventable diseases and concern from a small but vocal group of parents, activists, celebrities, and fringe investigators that vaccines regularly cause irreparable harm. Physicians find that they are spending more and more time convincing patients and parents of the benefits of vaccines and responding to media-fueled concerns about vaccine safety.

Stories about children whose parents claim were adversely affected by vaccines circulate widely in the community. Many of these accounts are heard on television talk shows, are mentioned in magazines, or find their way into conversation among friends. Similar stories and disparaging remarks about vaccines are constantly moving through Internet blogs, chat rooms, and message boards. News coverage of complex issues such as vaccine safety often leaves viewers with unanswered questions.

Concern about vaccine safety has also impacted the policymaking arena. Since 2002, a number of state legislatures have considered bills that would prohibit use of certain vaccines containing thimerosal (an ethylmercury-based preservative present in some injectable influenza vaccines). This activity was spurred by claims that thimerosal-containing vaccines contribute to the development of autism and other neurodevelopmental problems in children (see *The Vaccine Quarterly* 2008;1[1]:11; 2008;2[1]:7; 2008;2[2]:6–7). Unfortunately, 7 states—California, Delaware, Illinois, Iowa, Missouri, New York, and Washington—enacted such laws between 2004 and 2006. Multiple scientific studies have definitively refuted this theory.⁸ Armed with science, physicians and other advocates have helped educate policymakers about the importance of having unrestricted access to vaccines. Consequently, the number of new states proposing this type of legislation has declined and no further bills restricting access to thimerosal-containing vaccines have been enacted (see Table). This shows that advocacy can work.

Who Are the Immunization Advocates?

Historically, several professional organizations have spoken out for the health and safety of our nation's children, particularly with respect to the threat of infectious diseases. These include the American Academy of Pediatrics, American Medical Association, American Academy of Family Physicians, and Infectious Diseases Society of America. Recently, however, new advocacy groups have emerged to focus primarily on the issue of vaccines. Some of the major groups are listed below.

Every Child by Two

ECBT was founded in 1991 by Rosalynn Carter, the former First Lady, and Betty Bumpers, the wife of retired Senator Dale Bumpers,

WEBSITES	
All websites accessed September 2, 2008.	
AAP Childhood Immunization Support Program	http://www.cisimmunize.org
Centers for Disease Control and Prevention: Vaccines & Immunizations	http://www.cdc.gov/vaccines
Every Child by Two	http://www.ecbt.org
Families Fighting Flu	http://www.familiesfightingflu.org
Immunization Action Coalition	http://www.immunize.org http://www.vaccineinformation.org
The Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu
Meningitis Angels	http://www.meningitis-angels.org
National Meningitis Association	http://www.nmaus.org
National Network for Immunization Information	http://www.immunizationinfo.org
Parents of Kids With Infectious Diseases	http://www.pkids.org
Vaccine Education Center, Children's Hospital of Philadelphia	http://www.vaccine.chop.edu
Vaccine Ethics Center, University of Pennsylvania Center for Bioethics	http://www.vaccineethics.org
Voices for Vaccines	http://www.voicesforvaccines.org

States Considering Legislation to Restrict Thimerosal-Containing Vaccines by Year			
Bill Status	Number of State Legislatures		
	2003–2004	2005–2006	2007–2008
Under consideration	6	28	20
Enacted	2	5	0

in the wake of a measles epidemic that killed nearly 150 people in the U.S. The organization set out to raise awareness of the critical need for timely immunizations and to foster a systematic way to immunize all of America's children by age 2. To forward this agenda, ECBT enlists the support of elected officials and their spouses, concerned community leaders, and representatives of many national organizations.

Immunization Action Coalition

The IAC, established in 1991, is perhaps the nation's largest non-profit distributor of educational materials about immunization for both health professionals and the public. IAC also facilitates communication about the safety, efficacy, and use of vaccines within the broad community of patients, parents, health care organizations, and government health agencies.

The Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health

The Institute, established in 1997, provides an independent assessment of vaccines and vaccine safety to help guide decision-makers and educate physicians, the public, and the media about key issues surrounding the safety of vaccines.

National Network for Immunization Information

NNii is an affiliate of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics, American Nurses Association, American Academy of Family Physicians, National Association of Pediatric Nurse Practitioners, American College of Obstetricians and Gynecologists, University of Texas Medical Branch, Society for Adolescent Medicine, and American Medical Association. Its purpose is to advance education and science relating to vaccines and immunizations.

Vaccine Education Center, Children's Hospital of Philadelphia

The VEC was launched in October 2000 to provide parents and health care professionals with accurate, comprehensive, and up-to-date information about vaccines and the diseases they prevent. The Center, through its web sites, videos, informational tear sheets, and speakers' programs, seeks to dispel some of the common misconceptions and misinformation surrounding vaccines. Materials can be downloaded from the website or ordered at nominal cost.

Vaccine Ethics Center, University of Pennsylvania Center for Bioethics

The study of ethical issues associated with vaccines and vaccination programs has been a research focus of the Center for Bioethics since January 2005. The Center has identified and studied ethical challenges present throughout the vaccine life-cycle; organized regional, national, and international meetings; and contributed to scholarly and public dialogue on vaccine ethics and policy.

Voices for Vaccines

Launched in 2008 with the support of several allied organizations, this organization's primary mission is to demonstrate the broad base of support that vaccines have earned, both in the U.S. and internationally. The organization seeks members who support immunization and want opportunities to speak out in support of wise immunization policy. Membership is free, and laypersons and

health professionals are welcome to join. People who have personal or professional experience with vaccine-preventable diseases are particularly invited to share with others the potential consequences of not vaccinating.

Other organizations that post credible vaccine safety information on their web sites include the AAP Childhood Immunization Support Program and the Centers for Disease Control and Prevention.

Action Items

How can physicians and other health care providers be stronger immunization advocates? Here are some thoughts.

Provide Resource Materials to Patients

Since 1994, federal law has required all public and private providers of immunization services to give copies of Vaccine Information Statements (VISs) to every vaccinee (if a minor, to their parent or legal representative) before administering certain vaccines. The VISs provide basic information about the vaccine and the disease against which the vaccine protects, including the risks of the vaccine and the benefits of immunizing. You can download camera-ready copies of VISs, including translations in more than 30 languages, by visiting the IAC website.

For parents who would like to read more about these issues, or have specific concerns about vaccine safety, the IAC has developed a 1-page flyer that provides links to reliable websites and also has references for books and videos that are appropriate for parents.¹⁰ Clinicians may wish to keep copies of some of these materials in their offices to distribute to patients or parents who have questions. Alternatively, providers may wish to use them to develop their own materials to address the concerns most frequently raised by families. It is important to point out that parents really do need to be *directed*, because they may not be able to separate the wheat of valid science from the chaff of misinformation on their own.

Keep Up With the News

Vaccines and related issues are getting increasing media attention (see review of article by Smith et al. in this issue). Several organizations, including ECBT, IAC, and NNii, regularly post news stories on their web sites, and some operate LISTSERVs that send the information to your email in-box.

Join Other Pro-Vaccine Advocates

If you're not already a member, join your professional society. Follow the activities offered and attend noteworthy events if offered, such as advocacy or lobby days where legislators can hear from you on issues important to you and your patients. Many states and localities have formed coalitions to work on important immunization issues. While you may not have an extra hour in your day to attend a meeting, you can always get on the mailing list and join in when time permits. To find a coalition in your community, call your state health department⁹ or visit <http://www.izcoalitions.org>.

Be a Part of Voices for Vaccines

As sometimes occurs when an intervention like vaccination is generally accepted and becomes the status quo, the voices of those who oppose it are loud and get disproportionate media attention. Voices for Vaccines was formed to amplify the views of those who understand the importance of vaccination. Join up, make

(continued on page 6)

Learning Objectives: After reading the literature reviews in this issue, participating physicians with an interest in vaccination should be able to identify selections from the current literature of greatest value to their clinical practice and to incorporate the knowledge gained for better care of patients.

Effect of a School-Entry Vaccination Requirement on Racial and Ethnic Disparities in Hepatitis B Immunization Coverage Levels Among Public School Students.

Morita JY, Ramirez E, Trick WE.

PEDIATRICS 2008;121:E547–E552.

The purpose of this study was to evaluate the effect of Illinois's requirement for vaccination against hepatitis B before entry into fifth grade, a requirement that went into effect in 1997. The mandate allowed both permanent medical and religious exemptions and made a 1-year allowance for students who were in the process of completing the series at the time of fifth-grade entry. Chicago public school immunization coverage levels were retrospectively evaluated—both overall and by race/ethnicity—over the course of 6 consecutive years. The cohorts were students who entered grade 12 between 2000 and 2005; presumably, most had entered fifth grade between 1993 and 1998, thus spanning the years before and after the mandate was instituted. Students who dropped out before grade 12 were not included in the study.

The data were obtained from the Chicago public school system's electronic health database and included vaccination history (month and year of vaccination as well as medical or religious exemptions), date of birth, gender, and race/ethnicity (self-reported as black, white, Hispanic, Asian, or Native American). The main outcome of interest was the proportion of students who had received at least 3 doses of HepB by October of the assessment year. For example, a student who entered fifth grade in 1993 was considered fully vaccinated for hepatitis B if he or she had received all 3 doses by October 1993. The percent vaccinated at each grade level from grades 2 through 12 was also assessed. Comparisons were made between annual vaccination levels of pre-mandate cohorts (the four groups who entered fifth grade from 1993 to 1996) and post-mandate cohorts (the two groups who entered fifth grade in 1997 and 1998). Comparisons also were made between annual vaccination levels of white students and students of other large racial/ethnic groups, specifically black and Hispanic. Ninth grade was considered an important focus because hepatitis B is most frequently acquired during sexual intercourse, and approximately 25% of ninth graders reported having had vaginal intercourse.

The team evaluated records for 106,541 students; class cohort size grew each year from just less than 15,000 in the Class of 2000 to almost 20,000 in the Class of 2005. Using the 2005 American Community Survey population estimate, each cohort represented between 41% and 54% of Chicago residents who were 17 years of age. Race/ethnicity was stable throughout the period—in each class, 11% to 13% of the students were white, 50% to 51% black, and 30% to 34% Hispanic.

HepB coverage rates were significantly higher in the post-mandate cohorts than the pre-mandate cohorts each year from fifth-grade entry through twelfth-grade entry (Figure, page 6). For example, comparing the HepB coverage rates of the first post-mandate cohort (Class of 2004) with the last pre-mandate cohort (Class of

2003), the rates at fifth-grade entry were 38% vs 4% and at ninth-grade entry were 85% vs 37%. Comparisons of HepB coverage rates in the post- and pre-mandate cohorts by race/ethnicity showed that disparities decreased in the post-mandate cohorts (Table). Disparities between white and Hispanic children were eliminated for the second post-mandate cohort.

***This study found that in Chicago—a city whose HepB coverage rates were considerably below the 90% goal set out in Healthy People 2010—institution of a fifth-grade school entry requirement was associated with a rapid increase in uptake among those who remained in school until the twelfth grade. In addition, there was a diminution of the disparities that had existed between white children (who historically were better immunized) and black and Hispanic children. The authors point out, however, that coverage among students in the cohorts was likely to be higher than among their peers who left school before the twelfth grade and were, therefore, not included in the study. They also acknowledge that a small increase in immunization rates may have been due to an increase in the dropout rate (from 1996 through 2004, dropout rates in Chicago public schools ranged from 12.3% to 16.4%). Nonetheless, the association of school entry requirements with increasing vaccination levels was robust and consistent with other studies (see review of the article by Lopez et al. in this issue).**

The effectiveness of school mandates is predicated on several conditions that were in place for HepB vaccination in the Chicago area. Notably, the fifth-grade school entry requirement came 3 years after the ACIP, the AAP, and the AAPF had recommended routine HepB vaccination for adolescents.¹ Efforts to educate the community and health care providers about both the disease and the vaccine were in place, raising popular acceptance of the vaccine. Importantly, the authors point out that activities to increase access to immunization had already been instituted when the Illinois school entry requirement went into effect. These included provision of the vaccine for insured, uninsured, and underinsured children and school-based vaccination drives. Without these activities to ensure access, school-entry mandates may have an important unintended consequence: denying school entry to students with poorer access to health care. Barring such students from school may set off a cascade from which it is difficult to recover.

—Reviewed by Sharon G. Humiston, MD, MPH

Reference

- Centers for Disease Control and Prevention. MMWR 1995;44:574–575.

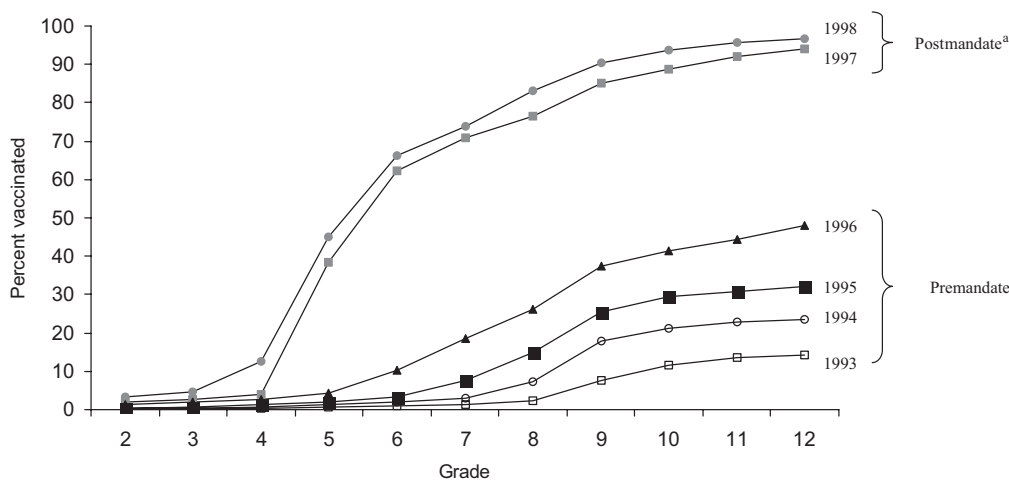
(continued on page 6)

Year	Fifth Grade			Ninth Grade		
	White	Black	Hispanic	White	Black	Hispanic
1996 (Pre-mandate)	8%	3%	4%	46%	32%	40%
1997 (Post-mandate)	46%	33%	42%	89%	84%	86%
1998 (Post-mandate)	50%	39%	51% ^a	93%	89%	93% ^a

^a Statistically equivalent to the value for white children.

Effect of a School-Entry Vaccination Requirement on Racial and Ethnic Disparities in Hepatitis B Immunization Coverage Levels Among Public School Students.

(continued from page 5)



HBV coverage levels according to grade for 6 consecutive cohorts of Chicago public school students before and after the state of Illinois required vaccination. ^aReceipt of HBV was required for entry into the 5th grade. Reproduced with permission from *Pediatrics*, Vol. 121, Page e549, Copyright © 2008 by the American Academy of Pediatrics.

Advocating for Safe and Effective Vaccines.

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your voice heard, and tell your colleagues and your patients about this valuable group too!

Refer Parents to Support Organizations

The real-life stories of children who have suffered or died from vaccine-preventable diseases painfully remind all of us of what can happen if we let our collective immunological guard down. Parents hear a lot about the harm that vaccines allegedly cause; they also need to hear about the dreadful diseases that children may get (utterly unnecessarily). In recent years, several groups have formed comprising families and physicians who have experienced first-hand what it is like to lose a child to a vaccine-preventable disease or to have a child who has experienced severe medical complications due to a vaccine-preventable disease. These groups can help families realize they are not alone. If you know a family in which a child or adult has experienced a vaccine-preventable disease, tell them about the organizations listed below, and encourage them to speak out.

Families Fighting Flu

This organization was established in 2004 to provide a forum for and support to families. The website posts stories of influenza-related loss and advocates for vaccination of all children.

Meningitis Angels

Meningitis Angels offers education, news, immunization advocacy, research on meningitis, and web pages filled with personal stories of courage, love, survival, and faith.

National Meningitis Association

This group provides education for families, medical professionals, and others about bacterial meningitis and prevention approaches to the disease.

Parents of Kids With Infectious Diseases

PKIDS assists families of children living with hepatitis, HIV/AIDS, or other chronic viral infections with emotional, financial, and informational support.

Have an Extra Hour or Two?

Write a letter to your local paper. This can be in response to a vaccine issue in the legislature or the media, or can simply remind the public of the value of vaccines. Volunteer to help on a legislative issue. Policymakers frequently face decisions on new school or child care immunization requirements, funding requests for immunization programs, and proposed restrictions on the use of vaccines. Your help may take the form of testifying at a public hearing or contacting the relevant city, county, state, or federal elected official.

Develop an Office Policy on Vaccination

Whether you choose to continue to see patients who refuse vaccines, or children whose parents refuse vaccines, having a well-thought-out, written statement that enunciates your office's reasons for recommending vaccines may serve to convince some hesitant individuals to be vaccinated in full and on schedule (see the Editor's Section in this issue regarding just such a policy). Maintain a dialogue about vaccines at every visit with those who remain out of compliance with vaccine recommendations.

The Last Word

The work that physicians and other health care providers do to protect children and adults from vaccine-preventable diseases is clearly making a difference in the health of our nation. We should not allow this remarkable achievement to be eroded by misinformation and misdirection. Continue to follow the science

(continued on page 10)

Epidemiology of Varicella Hospitalizations in the United States, 1995–2005.

Reynolds MA, Watson BM, Plott-Adams KK, Jumaan AO, Galil K, Maupin TJ, Zhang JX, Seward JF.

J INFECT DIS 2008;197:S120–S126.

Prior to the licensure of varicella vaccine (VARIVAX®) in 1995, varicella caused 11,000 to 13,500 hospitalizations and 100 to 150 deaths each year in the United States. While the greatest number of cases occurred in school-aged children, the highest rates of hospitalization were among adults and young infants. Varicella is more severe in adolescents, adults, and immunocompromised persons; however, 89% of persons hospitalized due to varicella or its complications did not have severe immune problems, and 70% had no comorbid conditions.

The Varicella Active Surveillance Project (VASP), initiated in 1995, has involved three sites: Antelope Valley in California, West Philadelphia in Pennsylvania, and Travis County in Texas (the latter site stopped surveillance in 1999). These sites, which collectively represent a cross-section of the U.S. population, actively sought cases of varicella in day care centers, schools, universities, public health clinics, hospitals, physicians' offices, correctional institutions, homeless shelters, large companies, and even some households. The current study was based on data gathered through this population-based project.

Varicella-related hospitalization was defined as admission to an inpatient ward or Emergency Department for > 8 hours within 14 days after rash onset, or beyond 14 days if the condition leading to hospitalization was a recognized complication of varicella (this included pneumonia, cerebellar ataxia, encephalitis, meningitis, soft tissue abscess, and cellulitis). Case patients meeting these "time-frame criteria" were excluded if the admission was for other diagnoses such as trauma, appendicitis, or asthma exacerbation.

From 1995 to 2005, 26,290 varicella cases were reported to the VASP. Of these, 219 potential cases of varicella-related hospitalization were identified, and 170 (78%) met the case definition. The overall hospitalization rate was 6.47 per 1000 cases of varicella, but a dramatic decline was noted over the years (Table 1). Between 1995 and 1998, children < 10 years of age accounted for 69% of hospitalizations and those ≥ 20 years of age accounted for 23%. From 1999 to 2005, the proportion of hospitalizations among those < 10 years of age dropped to 49% while that among adults ≥ 20 years of age increased to 32% ($P = 0.03$), even though the number of hospitalizations declined in all age groups. Over the entire 10-year study period, the hospitalization rates for children 5 to 9 years of age was 2.6 per 1000 cases of varicella; for infants < 1 year of age it was 20.9 and for adults ≥ 20 years of age it was 26.3 per 1000. The odds of being hospitalized were approximately 7 times higher among young infants and adults as compared to school-aged children.

Hospitalization was more likely in persons who had not been vaccinated and in immunocompromised individuals (Table 2). No

differences by gender or race/ethnicity were seen. Most (60%) hospitalized individuals were healthy before contracting varicella; 25% had a comorbid condition and 15% were immunocompromised. Eighty-five percent were admitted within the first week after rash onset, and the median length of hospital stay was 3 days (range, < 1–17).

The most common complications were skin and soft tissue infections or cellulitis, dehydration, and respiratory complications. The rates of these events in the overall population decreased over time, since the rates of varicella also decreased. However, the complication rates were unchanged among persons who actually got varicella.

***The incidence of varicella has decreased dramatically since the introduction of the vaccine. This population-based study substantiates a decline in varicella-related hospitalizations as well. The largest gains were among children (who were initially targeted for vaccination), but there have been declines in all age groups. Despite the decrease in hospitalizations, it is worth pointing out that one thing has not changed—infants, adolescents, and adults remain at highest risk.**

The most important finding in this study is that up to 60% of the observed hospitalizations were vaccine preventable. Hospitalization was 3 times higher among those who had not been vaccinated. Also, given the high risk for adults, the data suggest that more effort should be put into vaccination of varicella-susceptible adults.

The strength of this study lies in the fact that it is population-based and that the data were confirmed through review of medical records. Other studies have relied more on administrative data without clinical confirmation. Limitations include the inability to assess prior health information in all cases. There also could be some underestimation of hospitalization rates if persons living in the study regions were hospitalized elsewhere. Finally, some of the 10 asthma-related hospitalizations that were excluded as varicella-related cases could have been triggered by varicella infection.

The recommendations for a 2-dose varicella vaccine regimen (see The Vaccine Quarterly 2007;1[1]:13; 2007;1[4]:17) should further reduce varicella-related hospitalizations as breakthrough cases (and any complications associated with these) decline. This also will extend herd immunity protection to those who are not eligible to be vaccinated. There hopefully will come a day when varicella infections, and thus related hospitalizations, go the way of epiglottitis.

—Reviewed by Charles R. Woods, MD, MS

Time Period	Varicella-Related Hospitalization	
	Number	Rate per 100,000 Population
1995–1998 ^a	129	2.54 (2.1, 3.0)
1999–2001	26	0.80 (0.5, 1.2)
2002–2005	15	0.62 (0.4, 1.0)

^a Includes all three regions; subsequent time periods represent two regions.

	Rate of Varicella-Related Hospitalization per 1000 Varicella Cases	Odds Ratio for Hospitalization (95% CI) ^a
Vaccinated		
Yes	1.8	Reference
No	6.8	3.0 (1.1, 8.3)
Immunocompromised		
Yes	11.2	2.0 (1.3, 3.2)
No	7.7	Reference

^a Adjusted for region, gender, race/ethnicity, age, varicella vaccination, and immunocompromised state.

Factors Associated With Uptake of Measles, Mumps, and Rubella Vaccine (MMR) and Use of Single Antigen Vaccines in a Contemporary UK Cohort: Prospective Cohort Study.

Pearce A, Law C, Elliman D, Cole TJ, Bedford H, the Millennium Cohort Study Child Health Group.

BMJ 2008;336:754–757.

MMR was introduced in the United Kingdom in 1988. By 1992, vaccine coverage at 2 years of age was 92% (the first dose is currently recommended for children at 13 months of age in the U.K., and the second dose in the fourth year of life). In 1998, a paper published by Wakefield and colleagues in *The Lancet*¹ suggested that there was a link between MMR and autism. After publication of that paper, MMR vaccine coverage declined, bottoming out at 79% in 2003. Wakefield advocated that the MMR components be given as single vaccines at intervals of at least a year, prompting some parents to request separate injections of measles, mumps, and rubella vaccines.

This nationally representative cohort study was performed to estimate uptake of MMR and single antigen vaccines and to explore factors associated with uptake and reasons for not using MMR. The study population was a random sample of children born in the U.K. from September 2000 to January 2002. The main outcome measure was immunization status at 3 years of age, defined as “immunized with MMR,” “immunized with at least 1 single antigen vaccine,” or “unimmunized.”

Of the 14,578 children for whom immunization data were available, 88.6% were immunized, 5.2% had received at least 1 single antigen vaccine, and 6.1% were unimmunized. MMR uptake varied significantly by country, and was highest in Northern Ireland and lowest in England. Of the 634 children who had received at least 1 dose of a single antigen vaccine, 52% had been vaccinated against all 3 viruses and 7.4% had been vaccinated against only 1 disease.

Children were more likely to be unimmunized if they lived in a household with other children or only 1 parent, or if their mother was younger than 20 or older than 34 at the time of the child's birth, was more highly educated, or was self-employed or not employed. Use of single vaccines increased with household income (almost 3 times more likely for incomes > \$102,190 [U.S. dollars]), maternal age, and maternal education. Nearly three-quarters (74.4%) of parents who did not immunize with MMR made a conscious decision not to do so. Among the most common reasons given were that they were scared or thought the vaccine was too dangerous, fears over possible links to autism, and negative media attention.

**In many ways, we are victims of our own success. The vaccines our children receive, such as MMR, are so effective that the diseases are extremely rare. Most medical students and physicians training in the U.S. today have never seen measles. Not surprisingly, most parents have not either; they do not know anyone who has had measles, they do not understand its severity, and they are not afraid of the disease. Meanwhile, suggestions that MMR is associated with autism stoke concerns that the vaccine itself might harm their child. Fear of the vaccine has replaced fear of the diseases!*

It is interesting to look back at the 1998 Lancet paper. Wakefield and colleagues reported on 12 children referred to a pediatric gastroenterology unit who had both gastrointestinal symptoms (later shown mostly to be constipation) and pervasive developmental disorder characterized by a loss of previously attained developmental milestones. Eight of the 12 parents recalled that the onset of the developmental delay was within 2 weeks of the child receiving MMR. The theory proposed, as implausible as it sounds, was that the 3 live vaccine viruses replicating at the same time caused intestinal damage that released proteins that caused brain damage. This (or any) case series, of course, could not prove a link between vaccination and autism. And numerous subsequent studies have shown no link. But the damage was done. The publication generated significant publicity in the U.K., scared parents (and probably some doctors), and led to declines in MMR usage that ultimately led to outbreaks of measles and mumps.

While the paper stated that the 12 patients were “consecutively referred,” in reality almost all of the parents were clients or contacts of a legal firm that was pursuing litigation against the pharmaceutical companies that manufactured MMR. Rather than representing “random” consecutive patients, they were selected and referred precisely because they had gastrointestinal problems and autism that the parents claimed manifested after vaccination. In addition, Wakefield had undisclosed potential conflicts of interest with the firm.² Ultimately, the majority of the manuscript's authors “retracted their interpretation” of the findings in the paper.³

Although MMR uptake in the cohort in this study was high, a substantial proportion of children remained susceptible to vaccine-preventable infections, largely because parents consciously decided not to immunize. Receiving single antigen vaccines could not reduce the likelihood of autism, but did leave many of these children vulnerable to at least one or two of these diseases. Historically, children most likely not to be immunized are those of lower socioeconomic status who lack access to the health care system. As shown in this paper and others, underimmunization or nonimmunization has become a “disease” of affluence.

—Reviewed by Jay M. Lieberman, MD

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Media Coverage of the Measles-Mumps-Rubella Vaccine and Autism Controversy and Its Relationship to MMR Immunization Rates in the United States.

Smith MJ, Ellenberg SS, Bell LM, Rubin DM.

PEDIATRICS 2008;121;E836–E843.

A parent's willingness or desire to have his or her child vaccinated is influenced by a variety of factors, including their perception of the safety of the vaccines. The mainstream media are a major source of health information for many parents. For example, media coverage of a purported link between MMR and autism was associated with a sharp decline in measles vaccine uptake in the United Kingdom in the late 1990s. The current study was performed to assess the association between media coverage of the MMR–autism controversy and MMR immunization in the United States.

Annual MMR coverage was determined using National Immunization Survey (NIS) data from 1995 to 2004, which included > 215,000 children. NIS is a random-digit-dialing survey that estimates vaccine coverage among children 19 to 35 months of age as well as adolescents. (Media coverage was measured by looking at stories on MMR vaccine and autism using LexisNexis, a large database of national and local news media. The database includes stories from 295 newspapers in the U.S. (including 90 of the top 100 circulating papers), Associated Press releases, major television networks (ABC, CBS, NBC, Fox, and CNN), and National Public Radio broadcasts. The primary outcome measure was selective MMR nonreceipt, defined as those children who received all childhood immunizations except MMR. Factors associated with MMR nonreceipt were identified using a logistic regression model.

Selective MMR nonreceipt, which occurred in as few as 0.8% of children in the 1995 cohort, rose to 2.1% in the 2000 cohort (Figure). Children included in the 2000 survey were born when the hypothesized link between MMR and autism surfaced in the medical literature (in a 1998 article by Wakefield et al. that was

published in *The Lancet*; see review of article by Pearce in this issue), but before there was any real media attention in the U.S. Significant media coverage did not begin until 2001, and most of the coverage over the next several years was related to the 2001 Institute of Medicine Report on MMR and autism (which rejected a causal relationship at the population level) and two hearings held by the House of Representatives Committee on Reform. Selective MMR nonreceipt was more prevalent in private practices and was not related to family characteristics. MMR nonreceipt returned to baseline before sustained media coverage of the MMR–autism story began.

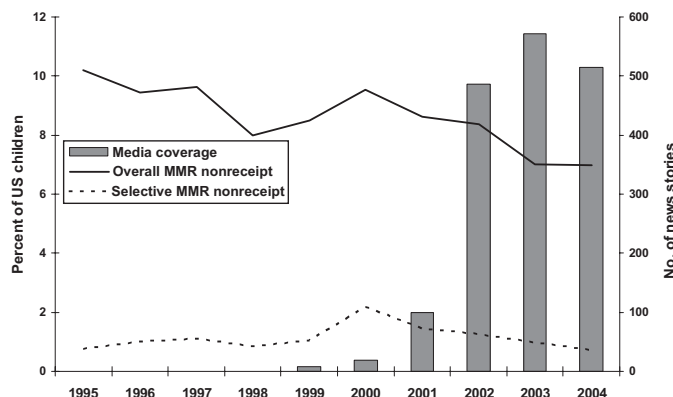
The authors conclude that while there was a significant increase in selective MMR nonreceipt temporally associated with publication of the original article suggesting a link between MMR and autism, this preceded media coverage of the MMR–autism controversy. They state this suggests a limited influence of mainstream media on MMR immunization in the U.S.

***The control of measles is one of the great triumphs of immunization. The number of reported measles cases in the U.S. (which significantly underestimated the actual number of cases) peaked at > 750,000 in 1958. The first live attenuated measles vaccine was licensed in 1963; MMR was first licensed in 1971 and recommended for all children. In 1989, a 2-dose regimen was adopted, and since 2000 annual reported measles cases have averaged < 100—in fact, measles is no longer considered endemic in the U.S. However, maintaining an absence of indigenous transmission is entirely dependent on maintaining high coverage levels, and there is no place for complacency. Case in point—in early 2008, outbreaks of measles in San Diego, Arizona, and New York City (among other places)¹ have served to remind us that measles remains a threat. These outbreaks began when travelers (5 U.S. residents and 5 visitors, all unvaccinated) brought the disease into the U.S., and the vast majority of cases occurred among children too young to be vaccinated or among those whose parents made a conscious decision to not vaccinate.**

Why do parents choose not to vaccinate against measles? Do negative news stories affect a parent's perceptions about vaccines and cause them to reject vaccination for their children? It is undeniable that what we see and hear in the media does influence us. When we see a commercial for a product, most of us do not go out and buy it, but enough of us do so that companies continue to advertise. Will all parents reject vaccines for their children because media reports suggest that vaccines are responsible for the increase in reported autism cases? No, but some will.

So why were these researchers unable to find a connection between media stories and MMR vaccine coverage rates, much different findings than were seen in the U.K.? One reason is that media coverage in the U.K. was intense after publication of the *Lancet* article, before multiple studies refuted claims of an association between MMR and autism. The media crush in the U.S. was later and smaller.

Another reason, I believe, that the authors found no link is that the definition of "media" was too narrow. The Internet has become a primary source of information (whether valid or invalid) about many topics, and this vast repository of information is not captured by LexisNexis. Google the term "vaccines"—you will get 15,700,000 hits, and many of the top results will be



MMR nonreceipt and media coverage according to NIS survey year. Overall MMR nonreceipt indicates children who did not receive the MMR vaccine; selective MMR nonreceipt, children who received 3 hepatitis B, 3 polio, 4 diphtheria-tetanus-acellular pertussis, and 3 *Haemophilus influenzae* type b vaccines but not the MMR vaccine; news stories, all newspaper stories, television programs, and radio programs that reported the MMR–autism controversy to which children in each year's NIS may have been exposed.

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blatantly anti-vaccine websites, with enough anecdotes and pseudo-science to frighten parents who are trying to “answer” the “vaccine question.” The authors dismiss the impact of the Internet in the 2000 cohort because “only” 35% of households had Internet access at the time. But even if only a relatively small percentage of those with Internet access believed the things they read, it could account for the small decline in vaccine coverage.

Finally, and fortunately, the media are only one potential influence on parents’ perceptions about vaccines. The primary determinant for most parents remains the health care provider (see *The Vaccine Quarterly* 2007;1[3]:14). If you are a strong advocate for immunizations, the majority of your patients will accept your recommendations to vaccinate. If, on the other hand, you are not convinced of the benefits or are concerned about potential adverse effects and therefore you do not make strong recom-

mendations, more parents will opt out. That immunization coverage in the U.S. has not plummeted in the face of very negative media coverage regarding MMR, thimerosal, and “too many shots” is testimony to the outstanding work pediatricians, family practitioners, nurses, nurse practitioners, and others have done to support and encourage immunizations. However, our workload has increased as we spend a lot more time talking to parents about vaccines and trying to convince them of their value and importance. It would be nice if the media would fairly and accurately report on vaccines instead of presenting sensationalized accounts that make our jobs more difficult.

—Reviewed by Jay M. Lieberman, MD

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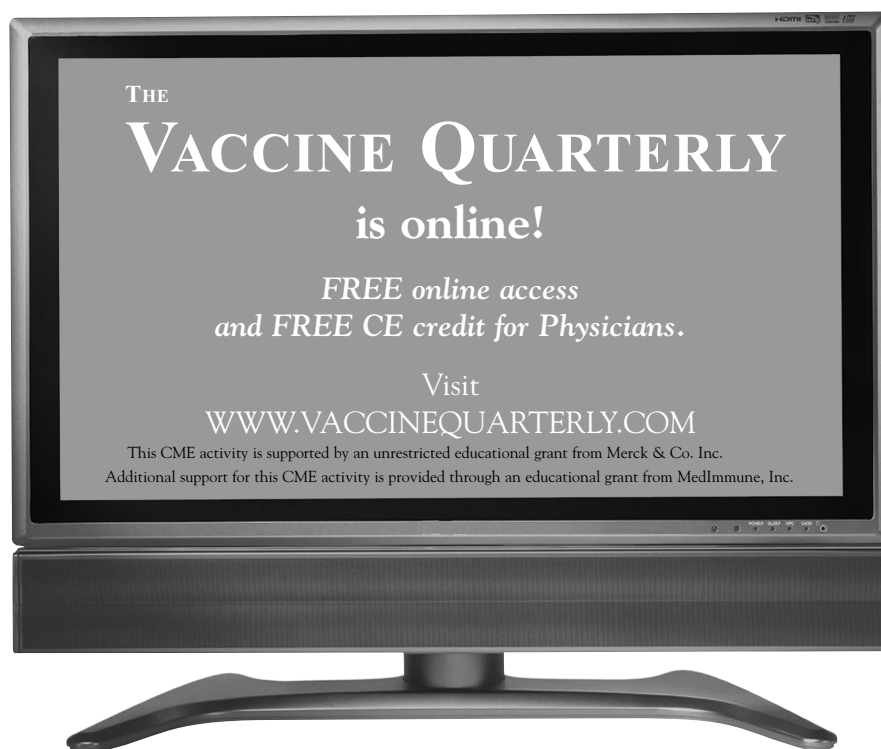
Advocating for Safe and Effective Vaccines.

(continued from page 6)

and advocate for immunization in your community and for your patients. It is the right thing to do.

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Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children.

France EK, Glanz J, Xu S, Hambidge S, Yamasaki K, Black SB, Marcy M, Mullooly JP, Jackson LA, Nordin J, Belongia EA, Hohman K, Chen RT, Davis R, for the Vaccine Safety Datalink Team.

PEDIATRICS 2008;121;E687–E692.

The Vaccine Safety Committee of the Institute of Medicine concluded in 1993 that there was a causal relationship between MMR vaccine and thrombocytopenia,¹ which made sense given the known association between wild-type measles infection and thrombocytopenia. Immune thrombocytopenic purpura (ITP) after administration of MMR has subsequently been reported in case series from Canada, France, Sweden, Finland, and the United States. However, these reports were limited by small numbers of patients, which made it difficult to define the true risk of ITP after MMR. They also failed to consider other possible causes of thrombocytopenia, such as pre-existing medical conditions or medications.

This study used the VSD to examine the association between MMR and ITP in more detail. Data from more than 2 million children ages 1 to 18 years were analyzed, covering the years 1991 to 2000. Thrombocytopenic children were identified by either documented abnormal platelet counts or ICD-9 diagnostic codes indicating thrombocytopenia without another cause. Cases of ITP were defined as having platelet counts $\leq 50,000/\mu\text{L}$ with other blood counts being normal and accompanied by clinical bleeding but not fever. Cases were excluded if in the previous 6 weeks the child either had an infection or was exposed to a medication that is known to be associated with thrombocytopenia. Children were also excluded if they were ill at the time of diagnosis or if the depressed platelet count was found incidentally. The only children who were included were those who were vaccinated with MMR while enrolled in the associated managed care organization and where clinical information was available for 1 year before and after.

A total of 1,036,689 children received MMR during the study period, 54% of whom were 12 to 23 months of age. A total of 1,673 potential cases were identified, with 259 patients meeting the case definition of ITP and 248 > 12 months of age. Only 5 children > 23 months of age had received MMR, so the main analysis focused on the 63 children 12 to 23 months of age. Among these children, 20 had received MMR within 42 days of diagnosis and 43 had not. There were no statistically significant differences in gender, platelet count, duration of illness, or occurrence of chronic ITP between the groups. The incident rate ratio (IRR; roughly, the ratio of the incidence of ITP in the exposed children divided by the incidence in the unexposed children) in children 12 to 23 months of age was 3.94–5.38, depending on the methodology used for calculation. The highest IRR (12.39–14.59) was seen in boys 12 to 15 months of age. Overall, 76% of cases of ITP among children 12 to 23 months of age could be attributed to MMR. The authors calculate that one case of ITP occurred for every 40,000 MMR vaccinations administered in that age group.

***The VSD is an active surveillance system created by the CDC in 1990 and operated by the CDC's Immunization Safety Office.² Information regarding immunizations, demographics, and medical outcomes is collected through large linked computerized data-bases from 8 health maintenance organizations. Approximately 6 million people of all ages are studied through this process, representing about 2% of the entire U.S. population. Given these numbers, relatively rare adverse events can be detected, unvaccinated control subjects can be stud-**

ied, and causal associations can be investigated.

This article represents an excellent example of the power of the VSD. Through the study of large population databases, accurate assessments of risk can be made. It is also a cogent reminder that vaccines are not 100% safe (for that matter, nothing in medicine [or life] is). This is easy to forget as we react to the barrage of unfounded vaccine safety concerns that takes place daily in the mainstream media (see review of article by Smith et al. in this issue).

Interestingly, one of the issues identified during this study was the lack of immunization documentation by clinicians who were evaluating patients with ITP. While medications and recent viral infections were documented, recent MMR administration was not routinely assessed. One upshot—clinicians should routinely ask about recent vaccinations when evaluating children with bruising and thrombocytopenia.

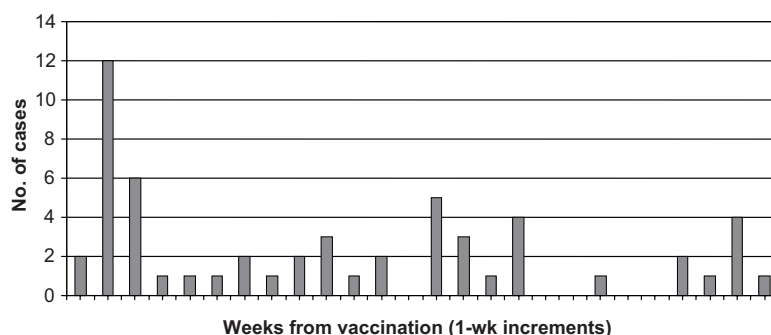
One wonders why boys seem to be at higher risk for ITP after MMR. One theory offered by the authors is that male toddlers may be more prone to evaluation for bruising, since they are more likely to suffer trauma than their female counterparts. This seems plausible, but the issue merits continued monitoring.

The VSD, along with the Vaccine Adverse Events Reporting System,³ the Clinical Immunization Safety Assessment Network,⁴ and the Brighton Collaboration,⁵ forms part of the vaccine safety net in the U.S. Clinicians and parents should be reassured that this system works—it detects even the smallest safety signals and it provides a rapid means to assess their significance.

—Reviewed by James H. Conway, MD

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Distribution of ITP cases according to weeks from MMR vaccination to ITP onset (12–23 months of age).

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Safety and Immunogenicity of Concurrent Administration of Live Attenuated Influenza Vaccine With Measles-Mumps-Rubella and Varicella Vaccines to Infants 12 to 15 Months of Age.

Nolan T, Bernstein DI, Block SL, Hilty M, Keyserling HL, Marchant C, Marshall H, Richmond P, Yogev R, Cordova J, Cho I, Mendelman PM for the LAIV Study Group.

PEDIATRICS 2008;121;508–516.

It is generally recommended to administer all vaccines that are due on a given day (using separate sites, of course).¹ To some extent, however, the interactions between simultaneously administered vaccines are unpredictable. This study therefore looked at the safety, tolerability, and immunogenicity of concurrent administration of LAIV—the intranasal live-attenuated influenza vaccine—and two subcutaneously administered viral vaccines—MMR, which contains live-attenuated measles, mumps, and rubella viruses, and varicella vaccine, which contains a live-attenuated varicella virus.

Healthy children 12 to 15 months of age who were up-to-date with routine immunizations were enrolled from 44 sites in the U.S. and 3 sites in Australia. Enrollment took place only during the seasons in each country where influenza does not typically circulate, in order to avoid the problem of distinguishing immune responses to the influenza vaccine from immune responses to natural infection. The list of exclusion criteria included those who had experienced one of the diseases that the vaccines are designed to prevent, receipt of any other vaccines within 2 weeks before or 30 days after enrollment in the study, history of allergy to eggs or vaccine components, recent febrile illness, recent aspirin treatment (there is the theoretical risk of Reye syndrome in patients who are taking aspirin at the time they receive the varicella vaccine or LAIV), known history of wheezing (a contraindication for LAIV), and blood product transfusion (which can blunt the immune response to live vaccines).

Children were randomized into 3 groups, as shown in Table 1. Serum specimens were obtained on day 0 and on day 42 (for meas-

urement of antibodies to measles, mumps, rubella, and varicella viruses in subjects who received MMR and varicella vaccine on day 0) and on day 72 (for measurement of antibodies to influenza virus in subjects who received LAIV on days 0 and 42).

A total of 1,251 children were randomized and 1,046 (84%) completed the study. Nearly equal numbers from each group were eliminated for various reasons, including 49 who were withdrawn because of a local measles outbreak! There were no differences in age, gender, or ethnicity between the groups.

More than 90% of evaluated subjects were seronegative for measles, mumps, rubella, and varicella at enrollment. As shown in Table 2, response rates to MMR and varicella vaccine were equivalent in those subjects who received LAIV concomitantly and those who did not. Similarly, responses to all 3 strains of influenza virus contained in LAIV were equivalent whether or not the subjects received MMR and varicella vaccine concomitantly.

All three regimens were well tolerated. As has been seen in previous studies and as might be expected, recipients of LAIV reported more nasal congestion and rhinorrhea compared to placebo (84% vs 77.6%). Also, children who received concurrent MMR, varicella vaccine, and LAIV experienced more fever (51.7% vs 29.1% for temperature > 100°F; 29.4% vs 13.9% for temperature > 101°F) and irritability (60.4% vs 51.5%) in the 10 days following immunization than those who received LAIV alone.

(continued on page 15)

Table 1. Study Design

Group	Number		Study Day		
	Assigned	Completed Protocol	0	42	72
1 (MMR/Varicella Vaccine)	411	362	MMR Varicella vaccine Intranasal placebo	LAIV	LAIV
2 (MMR/Varicella Vaccine/LAIV)	422	339	MMR Varicella vaccine LAIV	LAIV	Intranasal placebo
3 (LAIV)	412	345	LAIV	LAIV	MMR Varicella vaccine

Table 2. Immune Responses Among Initially Seronegative Subjects^a

Antigen	Group		
	1 (MMR/Varicella Vaccine)	2 (MMR/Varicella Vaccine/LAIV)	3 (LAIV)
Measles	97.1%	97.0%	—
Mumps	98.8%	96.7%	—
Rubella	97.4%	97.3%	—
Varicella	82.7%	88.3%	—
Influenza A (H1N1)	—	42.6%	43.7%
Influenza A (H3N2)	—	97.9%	98.3%
Influenza B	—	95.6%	92.1%

^a For measles, mumps, rubella, and varicella, seroresponse rates are given (this refers to the percentage of children who achieved a specific antibody level after vaccination). For influenza, seroconversion rates are given (this refers to the percentage of children who achieved a ≥ 4-fold increase in antibody level from baseline).

The Safety Profile of Varicella Vaccine: A 10-Year Review.

Galea SA, Sweet A, Beninger P, Steinberg SP, LaRussa PS, Gershon AA, Sharrar RG.

J INFECT DIS 2008;197:S165–S169.

Vaccine manufacturers generally conduct postmarketing surveillance for safety issues related to new vaccines. One example of such a surveillance system is Merck's Worldwide Adverse Experience System (MWAES), a passive surveillance program that receives voluntary reports from health professionals and consumers. Reports from the published medical literature are also added to the database. This study analyzes the 16,683 adverse events reported to the MWAES that were temporally associated with administration of varicella vaccine (VARIVAX®). The time period was from May 1, 1995 (shortly after licensure in the U.S.), to April 30, 2005, comprising the first decade of the vaccine's availability (approximately 55.7 million doses were distributed in 46 countries during that time period). Data from another company program, the Varicella Zoster Virus Identification Program (VZVIP), also were reviewed.

In this analysis, *breakthrough cases* of varicella were defined as a varicella-like rash in a vaccine recipient > 42 days after vaccination. *Secondary transmission* was defined as documentation of the varicella vaccine strain in nonvaccinated contacts of individuals who had been vaccinated. The VZVIP uses PCR analysis to distinguish between the vaccine strain and wild-type strains. Clinical specimens provided to the company were evaluated in the following clinical scenarios: (1) patients with > 50 vesicular lesions developing within 42 days of vaccination; (2) breakthrough cases of varicella; (3) herpes zoster; (4) varicella complicated by encephalitis, aseptic meningitis, cerebellar ataxia, or pneumonitis; and (5) suspected secondary transmission cases.

The adverse events reporting rate was 3.4 per 10,000 distributed doses of vaccine. There were 3,192 reports of rashes occurring within 42 days after vaccination: 65% occurred within 14 days of vaccination and 89% occurred within 21 days. The virus strain was determined in 79 cases through the VZVIP program. Wild-type strains were identified in 84% of cases occurring during the first 2 weeks after vaccination, while the vaccine strain was found in 83% with onset of rash 3 to 6 weeks after vaccination. Eight of 37 patients who had skin lesions caused by the vaccine strain were immunocompromised.

Breakthrough cases comprised 5,054 of the reports, for a rate of 0.9 per 10,000 doses distributed. Only 51 of these were considered "serious," and 38 were in immunocompromised hosts. There were 697 reports of herpes zoster; vaccine virus was identified in 57 cases and wild-type virus in 38. The median time from vaccination to onset for vaccine-related cases was 318 days, and 46% of cases involved the vaccine injection site.

One report described a child who was vaccinated at 2 to 3 years of age and developed leukemia at 4 years of age. While on chemotherapy he developed herpes zoster with mild meningeal signs, and the vaccine virus was identified in his CSF. Of 30 reports of neurological syndromes temporally associated with the vaccine that had CSF available for analysis, none were positive for the vaccine strain.

Three cases of secondary transmission were identified by the VZVIP. Each was a household contact of a 1-year-old who developed a rash after vaccination; 1 was a 30-year-old pregnant mother, 1 a 4-month-old sibling, and 1 a 35-year-old father. Two additional cases were reported with confirmation of vaccine virus infection in other laboratories. There were 7 reports of disseminated disease due to the vaccine strain, all of which occurred within

83 days of vaccination. Six of the patients were immunocompromised and 1 was a 48-year-old with Down's syndrome.

**This review of adverse event reports provides significant comfort regarding the safety of varicella vaccine. There were no unexpected events or "signals" in the submitted data. Passive data collection systems such as the MWAES have significant limitations, including under-reporting and inaccurate reporting. Nonetheless, such systems can provide insights into vaccine safety by virtue of what they do and do not receive. Information is collected from a wide range of medical practices and populations, including subgroups in which the vaccine has not been formally studied. Passive surveillance is especially useful for detecting rare adverse reactions that may go undetected in prospective clinical trials conducted before licensure.*

It is not surprising that breakthrough cases of varicella occurred (see The Vaccine Quarterly 2007;1[4]:11), but few cases were severe. Breakthrough disease is one of the reasons that a 2-dose strategy was adopted (see The Vaccine Quarterly 2007;1[4]:17). Secondary transmission appears to occur only when the vaccinee develops skin lesions, and there is no evidence that transmission causes harm. Herpes zoster in vaccine recipients most often develops within a year of vaccination and commonly occurs at the injection site. Disseminated disease due to the vaccine virus appears to occur exclusively in immunocompromised hosts. Neurological complications appear to be rare and are not linked to identification of the vaccine virus in the CSF of normal hosts.

The only other similar analysis of the varicella vaccine safety profile is from the U.S. Vaccine Adverse Event Reporting System (VAERS). Between March 1995 and July 1998, VAERS received 6,574 reports, for a rate of 6.75 per 10,000 doses.¹ The rate is higher than that obtained from the MWAES, probably because the reporting period was limited to the years right after licensure, when more VAERS reports tend to be submitted. Most of the VAERS reports were considered minor events, and serious risks were rare. Within the limitations of passive surveillance systems, these data provide significant substantiation of the safety of varicella vaccine when used in immunocompetent children.

—Reviewed by Charles R. Woods, MD, MS

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Status of School Entry Requirements for Varicella Vaccination and Vaccination Coverage 11 Years After Implementation of the Varicella Vaccination Program.

Lopez AS, Kolasa MS, Seward JF

J INFECT DIS 2008;197:S76–S81.

Varicella vaccine was licensed in the U.S. in 1995. Shortly thereafter, vaccination was recommended for all children 12 to 18 months of age, as well as susceptible persons < 13 years of age.¹ In 1999, the ACIP first recommended that states pass laws to require varicella vaccination for day care and elementary school entry.² In 2005, the ACIP expanded this to include middle school, high school, and college.³ The objective of the current study was to review the adoption of day care and school entry requirements and to determine the relationship between implementation of day care entry requirements and varicella vaccine coverage rates.

Data on entry requirements from each of the 50 states and the District of Columbia were obtained through annual contact with individual state health departments and by review of two Internet sites, the Immunization Action Coalition⁴ and the Sabin Vaccine Institute.⁵ Discrepancies between these resources were resolved through direct contact with state immunization program staff. States were grouped by the year they implemented day care entry requirements—before 2000, 2001 to 2002, and 2003 to 2005.

Annual vaccination coverage rates were obtained from the National Immunization Survey, a random-digit-dialing survey that is validated using health care provider records. Varicella vaccination coverage levels were categorized into three groups: ≥ 90%, 80% to 89.9%, and < 80%.

The number of states with entry requirements for day care, elementary school, and middle or high school increased from 1997 to 2006 (Figure, page 15). National varicella vaccine coverage rates for children 19 to 35 months of age increased from 25.8% in 1997 to 87.9% in 2005. In 2005, coverage rates ranged from 68.5% to 96.2%. Coverage was higher in states with day care entry requirements that were implemented earlier (Pearson’s correlation coefficient = -0.45; P = 0.002). In fact, states that implemented entry requirements in 2000 or earlier were more likely to have coverage rates of 90% or more when compared with states that implemented requirements during later periods. There also appeared to be an association between coverage rates and more extensive entry requirements (Table).

**Factors other than entry requirements may have contributed to the increase in varicella vaccination rates. For example, the VFC began providing the vaccine to eligible children in 1996, and State Children’s Health Insurance Plans also expanded access to varicella vaccination. While no effort was made in this study to look at these factors, it seems unlikely that they contributed selectively in states with broader entry requirements. Similarly, media coverage and health care provider training and education probably were more extensive in states that were anticipating expanded entry requirements, but this alone would have been*

unlikely to affect coverage rates in a major way. Given the robustness of the findings in this study, and the fact that other studies have demonstrated similarly strong relationships between school entry requirements and the uptake of vaccines (see review of the article by Morita et al. in this issue), a causal association seems likely.

This is an intuitive conclusion. However, the debate about entry requirements often centers around ethics (e.g., When is the loss of personal freedom and self-determination offset by a reduction in disease burden?) and risk shifting (e.g., Should children be required to accept future unknown risks for current protection?). In 2006, the Association of Immunization Managers produced a thought-provoking position statement on the requisites of day care and school mandates,⁶ which included the following concepts:

1. School and child care immunization requirements must be used sparingly, approached cautiously, and considered only after an appropriate implementation period. This allows for insurance and VFC coverage, public and health care provider acceptance of the vaccine, stable and adequate vaccine supply, addition to immunization information systems (registries), adequate assessment of safety, and significant enough uptake so as to reduce the compliance burden.
2. Vaccine mandates must be evaluated carefully, including epidemiologic, economic, and ethical concerns, because inappropriate application of a new mandate could undermine existing vaccination policies and programs.
3. School and child care requirements for any vaccine must be pursued through existing state processes, which are in place to ensure review by state immunization advisors, analysis of risk and benefit information, input from stakeholders, and consideration of related information.
4. Efforts to add or alter exemptions must be carefully coordinated with state immunization policy and goals. Opening existing laws or regulations for this purpose risks having an effective mandate weakened, altered in an undesirable way, or even revoked entirely.

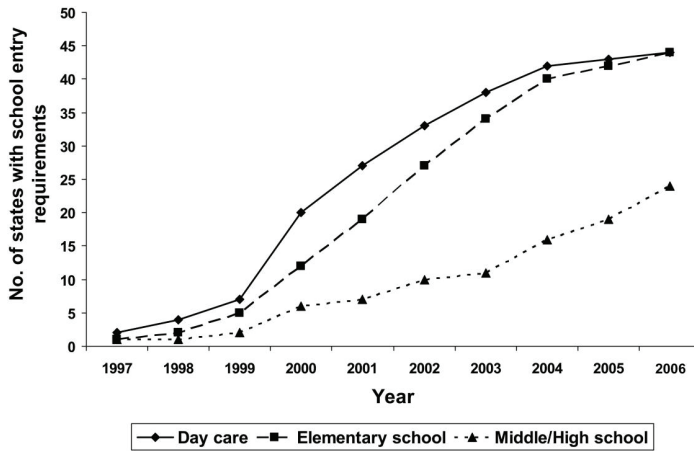
The broader perspective on immunization requirements summarized above is of great value as we approach an era when more vaccines are licensed and some familiar vaccines are more widely recommended. The truth is, school entry requirements hold both the potential for great good (e.g., disease prevention) and great disaster (e.g., undermining public and provider support of existing vaccine policy and recommendations).

—Reviewed by Sharon G. Humiston, MD, MPH

(continued on page 15)

Relationship Between Varicella Vaccination Requirements and Coverage Rates					
2005 Coverage Rate for Children 19 to 35 Months of Age	Number of States	Requirements at the Start of the 2006–2007 School Year			
		Day Care and Elementary School and Middle/High School	Day Care and Elementary School	Day Care or Elementary School Only	None
≥ 90%	10 ^a	7 ^a (70%)	3 (30%)	—	—
80% to 89.9%	35 ^b	14 (40%)	16 (46%)	4 (11%)	—
< 80%	6	2 (33%)	—	—	4 (67%)

^a Includes the District of Columbia.
^b One state with “elementary and middle school entry requirements only” is not shown.



No. of states with age-appropriate day care, elementary school, and middle and/or high school entry requirements for varicella vaccination, 1997–2006. Data for the District of Columbia, which implemented day care, elementary school, and middle and/or high school entry requirements in 1997, are not included. Although 43 states had implemented day care and elementary school entry requirements, data for the same states are not included in each group (2 states had implemented day care entry requirements only, and 2 states had implemented elementary school entry requirements only).

Reprinted with permission from The University of Chicago Press. Status of School Entry Requirements for Varicella Vaccination and Vaccination Coverage 11 Years after Implementation of the Varicella Vaccination Program. Lopez AS, Kolasa MS, Seward JF. *J Infect Dis* 2008;197:S76–S81. This article is in the public domain, and no copyright is claimed.

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Safety and Immunogenicity of Concurrent Administration of Live Attenuated Influenza Vaccine With Measles-Mumps-Rubella and Varicella Vaccines to Infants 12 to 15 Months of Age. (continued from page 12)

Influenza vaccination is now recommended for all children 6 months to 18 years of age (see Editor's Section). Since the vaccine is given yearly, providers will increasingly be in the position of delivering influenza vaccine to children who are also due for other vaccinations. LAIV (which is approved for use in healthy persons 2 to 49 years of age) is attractive because it is not a shot and because there is evidence that it provides broader coverage than TIV (see *The Vaccine Quarterly* 2007;1[3]:12).

Sequential administration of live vaccines in a short time frame can result in interference with the immune response; this was illustrated by the increased rate of breakthrough varicella that was seen when varicella vaccine was given within a month after MMR.² The exact mechanism for this is not clear, but probably has to do with replication of the first vaccine viruses interfering with replication of the second. The phenomenon can be seen as well when multiple live viral vaccines are administered at the same time. For example, immune responses were blunted when live-attenuated polio vaccine was given concomitantly with live-attenuated bovine rotavirus vaccine,

both of which were given orally.³

The current study should reassure providers that LAIV can be administered safely along with MMR and varicella vaccines. There is no evidence of major, clinically significant adverse events or reactions, although fever is more common. Immunogenicity is equivalent to sequential vaccination. The findings should help minimize missed opportunities to immunize children with influenza vaccine who are scheduled to receive any of their MMR or varicella vaccine doses. Remember, for kids to be optimally protected, every vaccination opportunity must be utilized!

—Reviewed by James H. Conway, MD

References

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- Centers for Disease Control and Prevention. MMWR 2001;50: 1058–1061.
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* Children < 9 years of age who are being vaccinated for the first time, or who were vaccinated for the first time in the previous season and only received 1 dose, need 2 doses separated by 4 weeks.

EDITOR'S SECTION

INFLUENZA VACCINE RECOMMENDATIONS

Vaccination recommendations for the 2008–2009 influenza season were published in July 2008.¹ The most significant change from previous years is the recommendation to vaccinate *all* children and adolescents from 6 months to 18 years of age (previously, vaccination was recommended for all children 6 to 59 months of age). The rationale behind this extension of the age range for routine vaccination was discussed by Dr. Kathryn Edwards in a previous issue of *The Vaccine Quarterly* (2007;1[4]:3–5). In essence, the goal of the influenza vaccination program has now moved beyond protecting individuals at risk for complications to actually affecting the epidemiology of transmission (by preventing spread among school-aged children and consequently their contacts).

The recommendations for high-risk children, such as those with chronic underlying medical conditions or immunosuppression, as well as children on long-term aspirin therapy and those residing in chronic care facilities, have not changed. Likewise, the recommendations for adults have not changed, including the recommendation to vaccinate all persons ≥ 50 years of age, women who will be pregnant during the influenza season, those with high-risk conditions, health care personnel, and residents of chronic care facilities. In addition, household contacts of persons who fall into any of the above categories should be vaccinated. This includes contacts of children < 5 years of age and adults ≥ 50 years of age.

LAIV or TIV may be used for healthy persons 2 to 49 years of age; only TIV should be used for all others. For the first time since 1978, when the trivalent vaccine came into routine use, all three strains in the vaccine have been changed; this is because of the poor match between last year's vaccine and the strains that circulated.

Since the recommendations technically include immunizing anyone who does not want to get influenza, the only people who should *not* be immunized are those who *cannot* be immunized (those < 6 months of age or those with contraindications) and those between 19 and 49 years of age who *want* to get the flu. It won't be long before annual vaccination is recommended for everyone.

Reference

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ZOSTER VACCINE RECOMMENDATIONS

Recommendations for use of the zoster vaccine (ZOSTAVAX®) were published in June 2008¹ (provisional recommendations were reported in *The Vaccine Quarterly* 2007;1[2]:15). About one-third of people will experience an episode of herpes zoster (shingles) in their lifetime, and nearly 20% of them will develop post-herpetic neuralgia, an often debilitating chronic pain condition. The zoster vaccine, by boosting pre-existing immunity to varicella zoster virus, can help maintain the virus in latency and prevent shingles. Overall efficacy in a large placebo-controlled trial was 51% against shingles and 67% against post-herpetic neuralgia.²

One dose of zoster vaccine should routinely be given to all individuals at 60 years of age. Vaccination is recommended for everyone ≥ 60 years of age who has not been immunized; this includes individuals who *do not* have a personal history of varicella and those *with* a history of shingles (it would seem prudent to wait a year after an episode of shingles since immunity will have been boosted by the episode). Patients with chronic medical conditions that are not associated with immunosuppression may be vaccinated. The vaccine is not indicated to treat zoster or post-herpetic neuralgia or to prevent post-herpetic neuralgia in patients who already have zoster.

Contraindications include allergy to any vaccine component, immunodeficiency or immunosuppression, and pregnancy (it can happen over 60!). If immunosuppression is anticipated, vaccination should occur at least 14 days earlier. Persons taking antiviral medications such as acyclovir, famciclovir, and valacyclovir should discontinue those medications at least 24 hours before vaccination and should remain off medication for at least 14 days. Receipt of antibody-containing blood products is not a contraindication to vaccination.

References

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RECOMMENDATIONS FOR TDAP IN PREGNANT AND POSTPARTUM WOMEN

Recommendations for the prevention of pertussis, diphtheria, and tetanus among pregnant and postpartum women and their infants were published in May 2008¹ (provisional recommendations were reported in *The Vaccine Quarterly* 2007;1[1]:13–14). The issues here are complicated. First, it has long been recommended that pregnant women be immune to tetanus in order to prevent tetanus in their newborns. Thus, women who had not received a tetanus booster in the previous 10 years were given Td during pregnancy. Second, it could be argued that women are at higher risk of getting pertussis than their infants are of getting tetanus (see *The Vaccine Quarterly* 2007;1[4]:14). Thus, boosting tetanus and pertussis immunity during pregnancy becomes an attractive prospect. However, there are no data regarding safety, immunogenicity, pregnancy outcomes, or protection of the infant against pertussis when Tdap is given during pregnancy. Furthermore, there is the theoretical possibility that transplacental antibodies could interfere with infant immunization.

Postpartum women who have never received Tdap should receive a dose before discharge from the hospital; this way, when they return to the community they will be protected from acquiring pertussis and transmitting it to their infants. The recommended interval since the last

dose of Td is 2 years, but shorter intervals may be used if there is no history of moderate-to-severe adverse reactions to previous doses of tetanus and diphtheria toxoid-containing vaccines. Women who are vaccinated should get their next Td booster 10 years later.

Pregnant women who are *not immune* to tetanus or who require a diphtheria booster should receive either Td or Tdap. Pregnant women who are *likely to be tetanus immune* should either receive Tdap or have vaccination deferred until after delivery, when they should receive Tdap (Tdap during pregnancy should be strongly considered if there is an increased risk of pertussis; in fact, the AAP favors giving Tdap to pregnant adolescents because they are at high risk²). Tetanus immunity is likely in the following situations:

- Women ≤ 30 years of age who received a complete childhood series of tetanus toxoid-containing vaccine *and* at least one booster as an adolescent or adult (the primary series in childhood consists of 4 or 5 doses and in adolescents and adults consists of 3 doses)
- Women ≥ 31 years of age who received a complete childhood series *and* at least 2 boosters, or who received a primary series as an adolescent or adult
- Tetanus antibody level ≥ 0.10 IU/mL

If Tdap is given during pregnancy, the second or third trimester is preferred. Remember, there are two Tdap products available: BOOSTRIX® (labeled for ages 10–18) and ADACEL® (indicated for ages 11–64).

One side note: in April 2008, the ACIP published a set of principles that will help to standardize the process of policy formation with regard to vaccination during pregnancy and breastfeeding.³ All new ACIP statements will include a background section on vaccination during pregnancy and breastfeeding, with explicit recommendations in standardized format and language.

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TWO NEW COMBINATION VACCINES LICENSED

The advantages of modern combination vaccines have been discussed previously (*The Vaccine Quarterly* 2007;1[2]:3–4). Now there is good news—two new combination vaccines were licensed in June 2008.

KINRIX™ is a fully liquid combination of DTaP (essentially INFANRIX®, which includes diphtheria and tetanus toxoids, inactivated pertussis toxin, filamentous hemagglutinin, and pertactin) and IPV (the same IPV that is in PEDIARIX®). It is labeled for the fifth dose of DTaP and the fourth dose of IPV in children 4 to 6 years of age, and it reduces the shot burden by 1 when compared to traditional component vaccines.

PENTACEL® is a combination of DTaP (one that is similar to DAPTACEL® and contains diphtheria and tetanus toxoids, inactivated pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3), Hib (ActHIB®, a polyribosylribitol phosphate-tetanus conjugate), and IPV (POLIOVAX®, which is licensed but not distributed separately in the U.S.). The vaccine must be reconstituted before use (the liquid DTaP-IPV is used to reconstitute the Hib, which is supplied lyophilized). PENTACEL® is labeled for children 6 weeks through 4 years of age and the usual schedule is 2, 4, 6, and 15 to 18 months of age. Children who receive 4 doses according to this schedule do not need further doses of Hib, but they do need a DTaP booster at 4 to 6 years of age. Since there is currently a shortage of Hib and it is recommended that the 12- to 15-month booster dose be deferred in otherwise healthy children,¹ only the first 3 doses of PENTACEL® should be given until further notice.² The fourth DTaP dose should be given at 15 to 18 months as a traditional component vaccine, and the fourth IPV dose should be given at 4 to 6 years of age. However, PENTACEL® may be used for the booster dose of Hib in high-risk children as early as 12 months of age (in this case a dose of DTaP at 15 to 18 months is not necessary).

Technically, 4 doses of PENTACEL® complete the childhood schedule of IPV; however, in some states a booster dose at 4 to 6 years of age may still be required. Official guidance on this from the ACIP is pending. PENTACEL® reduces the total shot burden by 7 if ActHIB® is currently in use. It reduces the shot burden by 6 if the office currently uses PedvaxHIB®, because a dose of that vaccine is not given at 6 months of age, and therefore one less shot is saved.

Remember, combination vaccines are *preferred* to traditional component vaccines.³

References

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3. American Academy of Pediatrics. *Pediatrics* 1999;103:1064–1077.

WHITHER ROTAVIRUS DISEASE?

Anyone notice that there were fewer infants with fever, vomiting, and diarrhea this winter? RotaTeq® was licensed in February 2006, and the recommendation for use in all infants at 2, 4, and 6 months of age was published in August of that year. The CDC recently analyzed rotavirus activity for the 2007–2008 season using data from the National Respiratory and Enteric Virus Surveillance System and the New Vaccine Surveillance Network.¹ In the previous 15 seasons, rotavirus activity usually began in mid-November; this past season it began in late February. In addition, the proportion of rotavirus tests that were positive this season was lower than the lowest proportion seen in the last 15 years. At peak season this year (which occurred at the end of April), only 17.8% of tests were positive, compared with a median of 41.0% at peak (which occurred in March) for the last 15 seasons.

This year, rotavirus season was delayed and diminished in magnitude. These benefits were seen despite the fact that, at best, less than half of infants had received 3 doses of the vaccine.² Hopefully, with increased uptake and with the introduction of another vaccine (ROTARIX®; see *The Vaccine Quarterly* 2008;2[2]:16), this trend will continue.

References

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MEASLES OUTBREAKS

In its heyday, before a vaccine was available, measles caused an average of 530,217 reported cases of illness (the true number was probably 3 to 4 million) and 440 deaths each year (see *The Vaccine Quarterly* 2008;2[2]:12–13). The first live measles vaccine was licensed in 1963 and MMR was licensed in 1971. By 1983, the number of cases had fallen to about 1,500. A resurgence of disease occurred between 1989 and 1991, with almost 56,000 reported cases and 123 deaths. Contributing factors were pockets of low vaccine coverage in the population and primary vaccine failure—the fact that 2% to 5% of children fail to respond to a single dose of MMR. In addition, infants < 1 year of age were probably more susceptible than in previous eras because their mothers had vaccine-induced immunity rather than natural immunity, and the amount of transplacental antibody they received was lower. The resurgence prompted the switch from a single-dose regimen to a 2-dose vaccine regimen, and by 2000 measles was determined to be no longer endemic in the U.S.¹

What does this mean? It means that there are not enough indigenous cases occurring to sustain transmission within communities. It does not mean that measles is absent. In fact, from January through July of 2008, 131 measles cases were reported.² Of these, 17 were directly imported from other countries and 99 were epidemiologically or virologically linked to imported cases (the source for 15 cases could not be determined). Most of the cases occurred during outbreaks in Illinois, New York, Washington, Arizona, and California, and 11% of the patients were hospitalized. U.S. residents accounted for 123 of the cases, 80% of whom were < 20 years of age and 91% of whom were unvaccinated or had unknown vaccination status. Sixty-six percent of those who were eligible for vaccination were not vaccinated because of philosophical or religious beliefs.

Unvaccinated children tend to be socially or geographically clustered, a factor that increases the risk of outbreaks. All it takes is for a case to arrive from overseas and an outbreak may ensue. This experience underscores the importance of maintaining immunization rates despite the absence of endemic disease. In addition, it illustrates the very real possibility that measles could once again become endemic in the U.S., as it has in the U.K.³

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3. Eurosurveillance Editorial Team. Measles once again endemic in the United Kingdom. *Euro Surveill* 2008;13:1. Available at: <http://www.eurosurveillance.org/viewarticle.aspx?articleid=18919>. Accessed September 2, 2008.

ALL STAR PEDIATRICS MANIFESTO

As discussed on several occasions in *The Vaccine Quarterly* (including the article by Diane Peterson in this issue), more and more parents are “asking the vaccine question,” and many are outright refusing to vaccinate their children—their fears of vaccination fueled by testimonials from celebrity “experts” and pseudoscientific misinformation that pervades the Internet. Part of our duty is to answer their questions, clarify the science, and advocate for vaccination as one of the best things a parent can do to protect his or her child. All of this takes time, such that what used to be a 30-minute well-child check is now an hour-long ordeal.

All Star Pediatrics, a pediatric group in Lionville, Pennsylvania, developed a beautifully simple, concise, and direct policy statement that explains to parents exactly where the practice stands on “the vaccine controversy.” The statement is reproduced in its entirety on page 19. It can also be found on their web site¹ or downloaded from the American Academy of Pediatrics web site.²

The statement affirms the group’s beliefs that vaccines are critical to children’s health, that they do not cause autism, and that reductions in vaccine coverage can have tragic results. It acknowledges parents’ concerns and affirms the practice’s commitment to “do everything we can to convince you that vaccinating according to the schedule is the right thing to do.” However, it also (in no uncertain terms) makes clear their belief that “by not vaccinating your child you are taking selfish advantage of thousands of others who do vaccinate their children,” referring to the herd immunity that keeps vaccine-preventable diseases at bay. Finally, the statement draws a clear line in the sand: “if you should absolutely refuse to vaccinate your child despite all our efforts, we will ask you to find another health care provider who shares your views. We do not keep a list of such providers, nor would we recommend any such physician.”

What should providers do when, despite their best efforts, families still refuse all vaccinations? The AAP has developed a *Refusal to Vaccinate* form³ that can be signed by the parent. The purpose of this form, aside from documenting the provider’s efforts to communicate the true risks and benefits of immunization, is to encourage parents to rethink the issue (it is not clear what, if any, legal protection this form would afford the provider should there be a bad outcome in a child who was not vaccinated). Some parents want a modified schedule for their children or want to pick and choose among the vaccines—in these situations, providers need to decide if they are willing to negotiate. The end (a fully immunized child) may justify the means, but negotiation also places a burden on the provider to prioritize the shots. Deferral of any given vaccine prolongs the period of vulnerability to the disease; in the case of polio, this may not be consequential (because polio has been eliminated from the Western Hemisphere), but in the case of, say, pertussis (which is still out there), the consequences may be serious.

The AAP takes the position that negotiation is in the best interest of the child.⁴ However, there is no law that says a provider must acquiesce to a parent’s wishes. Some providers feel that negotiation is a slippery slope—what if the next request is for half doses, or worse yet homeopathic ones? Others may feel that drawing a line in the sand is the best way to send the message that vaccinations—according

to the recommended schedule—are a critical component of pediatric care.

Ultimately, failure to see eye-to-eye about immunizations may be indicative of a lack of mutual trust between provider and parent, and this could affect the care of the child in other ways. Section E-8.115 of the American Medical Association Code of Ethics offers that physicians have the option of withdrawing from a case, as long as notice is given far enough in advance so as to permit other medical care to be secured.⁵

Providers will need to decide whether to retain in their practices patients who refuse all immunizations. Bear in mind that there are risks; on the other hand, retention allows continued opportunities to break down barriers. Moreover, it protects the family from seeking care from chiropractors and alternative medicine practitioners.

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5. American Medical Association Council on Ethical and Judicial Affairs. Termination of the physician-patient relationship. In: *Code of Medical Ethics: Current Opinions 2002–2003* ed. Chicago, IL: American Medical Association; 2002:110. Available at: <http://www.ama-assn.org/ama/pub/category/2498.html>. Accessed September 2, 2008.

All Star Pediatrics Vaccine Policy Statement

We firmly believe in the effectiveness of vaccines to prevent serious illness and to save lives.

We firmly believe in the safety of our vaccines.

We firmly believe that all children and young adults should receive all of the recommended vaccines according to the schedule published by the Centers for Disease Control and the American Academy of Pediatrics.

We firmly believe, based on all available literature, evidence and current studies, that vaccines do not cause autism or other developmental disabilities. We firmly believe that thimerosal, a preservative that has been in vaccines for decades and remains in some vaccines, does not cause autism or other developmental disabilities.

We firmly believe that vaccinating children and young adults may be the single most important health-promoting intervention we perform as health care providers, and that you can perform as parents/caregivers. The recommended vaccines and their schedule given are the results of years and years of scientific study and data gathering on millions of children by thousands of our brightest scientists and physicians.

These things being said, we recognize that there has always been and will likely always be controversy surrounding vaccination. Indeed, Benjamin Franklin, persuaded by his brother, was opposed to smallpox vaccine until scientific data convinced him otherwise. Tragically, he had delayed inoculating his favorite son Franky, who contracted smallpox and died at the age of four, leaving Ben with a lifetime of guilt and remorse. Quoting Mr. Franklin's autobiography:

In 1736, I lost one of my sons, a fine boy of four years old, by the small pox. . . I long regretted bitterly, and still regret that I had not given it to him by inoculation. This I mention for the sake of parents who omit that operation, on the supposition that they should never forgive themselves if a child died under it; my example showing that the regret may be the same either way, and that therefore the safer should be chosen.

The vaccine campaign is truly a victim of its own success. It is precisely because vaccines are so effective at preventing illness that we are even discussing whether or not they should be given. Because of vaccines, many of you have never seen a child with polio, tetanus, whooping cough, bacterial meningitis or even chickenpox, or known a friend or

family member whose child died of one of these diseases. Such success can make us complacent or even lazy about vaccinating. But such an attitude, if it becomes widespread, can only lead to tragic results. Over the past several years many people in Europe have chosen not to vaccinate their children with the MMR vaccine after publication of an unfounded suspicion (later retracted) that the vaccine caused autism. As a result of underimmunization, there have been small outbreaks of measles and several deaths from complications of measles in Europe over the past several years. Furthermore, by not vaccinating your child you are taking selfish advantage of thousands of others who do vaccinate their children, which decreases the likelihood that your child will contract one of these diseases. We feel such an attitude to be self-centered and unacceptable.

We are making you aware of these facts not to scare you or coerce you, but to emphasize the importance of vaccinating your child. We recognize that the choice may be a very emotional one for some parents. We will do everything we can to convince you that vaccinating according to the schedule is the right thing to do. However, **should you have doubts, please discuss these with your health care provider in advance of your visit.** In some cases, we may alter the schedule to accommodate parental concerns or reservations. **Please be advised, however, that delaying or "breaking up the vaccines" to give one or two at a time over two or more visits goes against expert recommendations, and can put your child at risk for serious illness (or even death) and goes against our medical advice as providers at All Star Pediatrics.** Such additional visits will require additional co-pays on your part. Furthermore, please realize that you will be required to sign a "Refusal to Vaccinate" acknowledgement in the event of lengthy delays.

Finally, if you should absolutely refuse to vaccinate your child despite all our efforts, we will ask you to find another health care provider who shares your views. We do not keep a list of such providers, nor would we recommend any such physician. Please recognize that by not vaccinating you are putting your child at unnecessary risk for life threatening illness and disability, and even death.

As medical professionals, we feel very strongly that vaccinating children on schedule with currently available vaccines is absolutely the right thing to do for all children and young adults. Thank you for your time in reading this policy, and please feel free to discuss any questions or concerns you may have about vaccines with any one of us.

