Making Immunization Policy in the United States

National Immunization Program
China Center for Disease Control

Beijing, China

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WPRO, World Health Organization

Outline

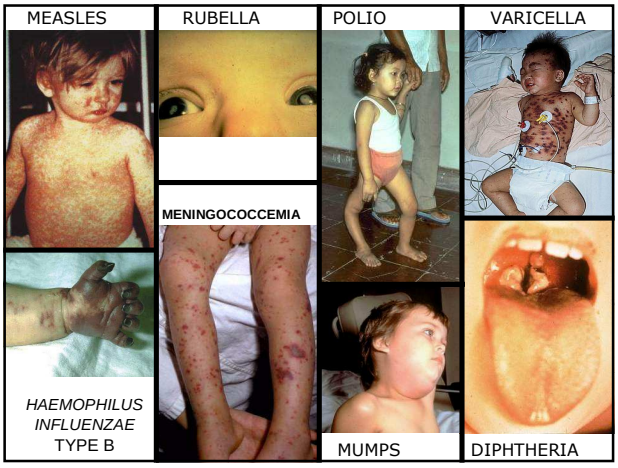
- Key policy questions asked of US CDC
- Special role of the Advisory Committee on Immunization Practices (ACIP)
- Examples
- Strengths, weaknesses, challenges of the US CDC immunization policy system

Critical questions and structures to obtain evidence

CDC'S VACCINE POLICY NEEDS

Key CDC Responsibilities

- Optimize use of vaccines to control and prevent VPDs with evidence
  - Burden of disease
  - Impact of vaccines
  - Changes in epidemiology
  - Safety of vaccines
- Fulfill a vaccine entitlement to vulnerable children



Events Requiring New Policy (1)

- Newly licensed vaccine
- New vaccine efficacy or effectiveness data
- Changes in disease epidemiology
- New signal from safety monitoring systems

Events Requiring New Policy (2)

- Vaccine shortage
- Unexpected disease outbreaks

The occurrence of these events drives CDC's vaccine policy agenda

Policy Evidence Needs and Organizations Responsible

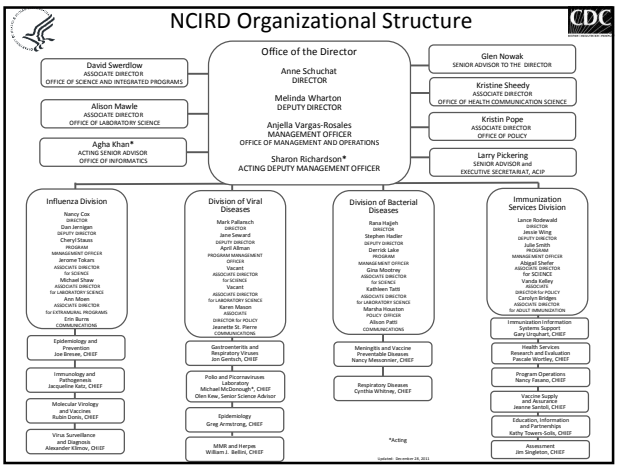
Type of evidence	Responsible organization
Licensing vaccine	Food and Drug Administration (FDA)
Determining vaccine efficacy	Manufacturer, FDA
Determining burden of disease	CDC/NCIRD viral and bacterial divisions
Monitoring vaccine effectiveness	CDC/NCIRD viral and bacterial divisions
Monitoring epidemiology of disease	CDC/NCIRD viral and bacterial divisions
Analyzing outbreaks	CDC/NCIRD viral and bacterial divisions
Monitoring vaccine supply	CDC/NCIRD immunization services, FDA
Monitoring safety of vaccines	CDC and FDA – Immunization Safety Office

Federal and State Roles

- U.S. immunization policy is made centrally
- States are responsible for surveillance, outbreak management, program implementation and management
- CDC provides guidance and funding, and works closely with states on all aspects of their program responsibilities

Structures for Monitoring Vaccine Impact

- Active surveillance
  - Burden of disease assessment
  - New vaccines that require special study sites
  - Vaccine safety (Vaccine Safety Datalink)
  - Monitoring vaccination coverage levels
- Passive surveillance
  - Older VPDs that have mandatory reporting
  - Vaccine safety (Vaccine Adverse Event Reporting System)
- These structures are led and funded primarily by CDC



Authorized by law in 1964

SPECIAL ROLE OF ACIP

ACIP Purpose

- Provides advice to Department of Health and Human Services and CDC that will lead to a reduction of VPDs in the U.S.
- Develops technical recommendations for licensed vaccines for use in civilians
  - Ages of vaccination, number of doses, etc.
  - Precautions, contraindications
- Has legal authority to mandate vaccine financial coverage
  - Public sector Vaccines for Children entitlement program
  - Private insurance for people of all ages

ACIP Characteristics

- Committee of 15 experts in public health and medicine
- Ex Officio membership for other federal agencies
- 25 liaison members for key stakeholder organizations
- Agenda set by CDC and working groups staffed by CDC
- Public meetings, 3 times each year

Technical Vaccine Recommendations

- Key questions
  - Should a vaccine be recommended for widespread use?
  - Does the benefit of the vaccine outweigh its risks and costs?
- Evidence considered
  - Licensed indication and schedule
  - Preventable burden of disease
  - Vaccine efficacy overall and in risk groups
  - Risks of the vaccine
  - Cost effectiveness
- These questions are re-evaluated as new evidence becomes available

Standardizing Methodology

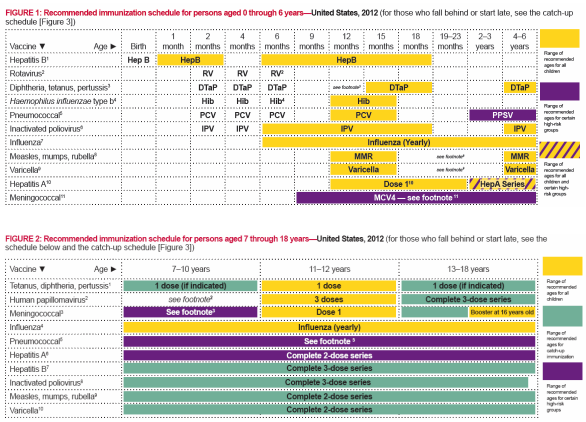
- Economic studies
  - Requires CDC approval to present before ACIP
  - Standard methods and assumptions on CDC/ACIP web site
  - Adopted in 2008
- GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)
  - Adopted in 2010; consistent with WHO use of GRADE
  - Evaluates the quality of evidence
  - Category A: for everyone in age or risk group
  - Category B: for individual clinical decision making only

Harmonization and Acceptance

- ACIP recommendations are harmonized with private sector professional groups
- ACIP recommendations must be accepted by the CDC director before they are in effect
  - Signaled by publication in CDC's MMWR

Implication of Recommendation

- ACIP recommendations become the standard of medical care in the U.S.
- ACIP recommendations become mandates for private insurance coverage of vaccines
  - Must cover all costs: vaccine and its administration
- ACIP resolutions are mandates for the inclusion into the Vaccines for Children entitlement program
  - Funding for vaccine purchase is immediate and automatic
  - CDC must negotiate vaccine contract for purchase of vaccine before it can be made available

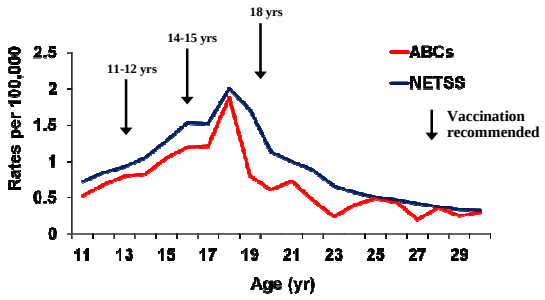


EXAMPLES OF POLICY MAKING

ACIP votes only after the vaccine is licensed

NEW VACCINE AGAINST A NEW VPD

Rates of Meningococcal Disease (A/C/Y/W135) by Age, 11-30 yr, United States, 1991-2002

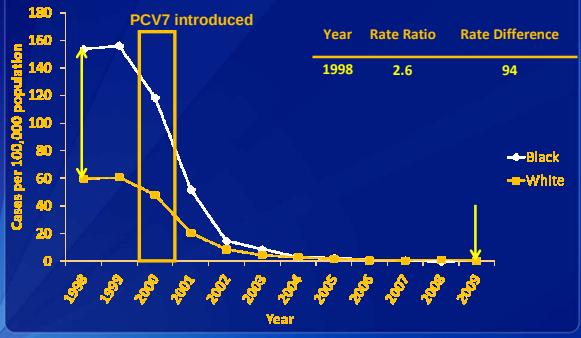


Requires ongoing monitoring of vaccine impact

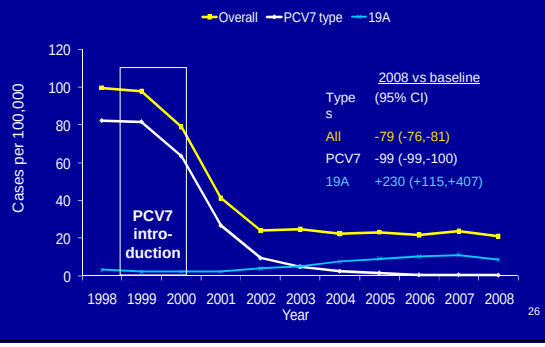
NEW MEASURE OF EFFECTIVENESS

2000 ACIP recommendation was for 7-valent PCV, the licensed vaccine

Rates of IPD in Children <5 years Caused by PCV7 Serotypes, by Race – ABCs, 1998-2009



Rates of Invasive Pneumococcal Disease among Children <5 years old, 1998-2008



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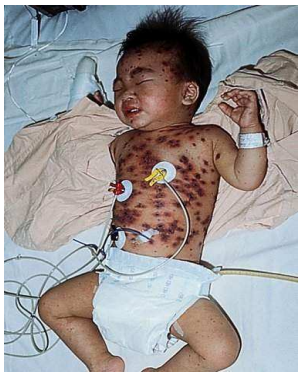
Recommendations and Reports December 10, 2010 / Vol. 59 / No. RR-11

Prevention of Pneumococcal Disease Among Infants and Children — Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)



1995 ACIP varicella recommendation was 1 dose at 15 months of age

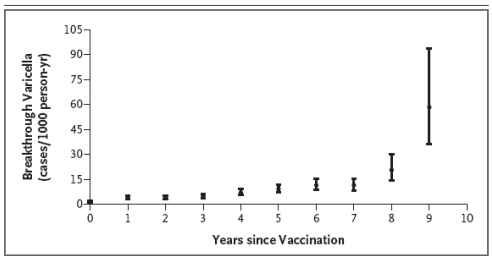
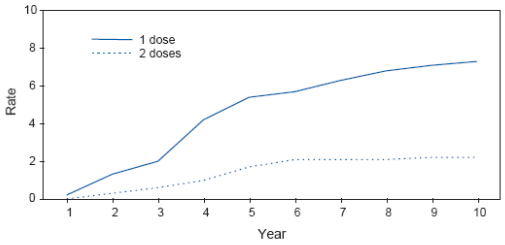


Figure 3. Adjusted Rates of Breakthrough Varicella among Children Vaccinated between the Ages of 12 Months and 12 Years, According to the Year after Vaccination.

Rates of disease were adjusted for the age at disease onset and the calendar year with the use of a Poisson regression model. All 95% confidence intervals, which are indicated by I bars, were calculated with the use of the Wald chi-square test.

Chaves et al. NEJM 2007; 356;11

FIGURE 4. Cumulative breakthrough rates* for 1 and 2 doses of single-antigen varicella vaccine among children aged 12 months–12 years, by number of years after vaccination — United States, 1993–2003



Source: Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J 2004;23:132–7.
* Per 100 person-years at risk.

Recommendations and Reports June 22, 2007 / Vol. 56 / No. RR-4

Prevention of Varicella

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Routine Vaccination

Persons Aged 12 Months–12 Years

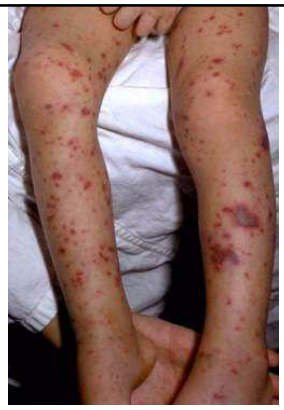
Preschool-Aged Children

All healthy children should receive their first dose of varicella-containing vaccine routinely at age 12–15 months.

School-Aged Children

A second dose of varicella vaccine is recommended routinely for all children aged 4–6 years (i.e., before entering prekindergarten, kindergarten, or first grade). However, it may be administered at an earlier age provided that the interval between the first and second dose is >3 months.

Because of the risk for transmission of VZV in schools, all children entering school should have received 2 doses of varicella-containing vaccine or have other evidence of immunity to varicella (see Evidence of Immunity).



2005 ACIP MCV4 recommendation was 1 dose at 11 or 12 years of age

Preliminary Menactra Vaccine Effectiveness Estimates, Duration of Protection*

Cases*	VE (95% CI) All cases (n=107)
Vaccinated <1 year	94% (14,99%)
Vaccinated 1 - <2 years	83% (1,97%)
Vaccinated 2 - <5 years	56% (-74, 89%)

* Controlling for underlying illness and smoking. Based on paperwork received by October 20, 2010

TABLE 1. Summary of serogroup C bactericidal antibody persistence as determined by serum bactericidal activity (SBA) 2–5 years after vaccination with Menveo and/or Menactra

Age group (yrs) at vaccination	Years postvaccination	Serogroup C SBA	Vaccine	No. of vaccine recipients in study	% of recipients with protective antibody levels
11 through 18*	2	% hSBA ≥1:8	Menveo	273	62
			Menactra	185	58
11 through 18†	3	% hSBA ≥1:4	Menactra	52	35
			MPSV4	48	35
11 through 18§	3	% brSBA ≥1:128	Menactra	71	75
			MPSV4	72	60
2 through 10§	5	% brSBA ≥1:128	Menactra	108	55
			MPSV4	207	42
11 through 18§	5	% brSBA ≥1:128	Menactra	16	56
			MPSV4	10	60

Abbreviations: hSBA = SBA using human complement; brSBA = SBA using baby rabbit complement; MPSV4 = quadrivalent meningococcal polysaccharide vaccine.

* Source: Gill C, Baxter R, Anemona A, Ciavarro G, Dull P. Persistence of immune responses after a single dose of Novartis meningococcal serogroup A, C, W-135 and Y CRM-197 conjugate vaccine (Menveo) or Menactra among healthy adolescents. Human Vaccines 2010;6:881–7.

† Source: Vu DM, Welsch JA, Zuno-Mitchell P, Dela Cruz JV, Granoff DM. Antibody persistence 3 years after immunization of adolescents with quadrivalent meningococcal conjugate vaccine. J Infect Dis 2006;193:821–8.

§ Source: Proceedings of the Advisory Committee on Immunization Practices (ACIP) meeting, June 2009.

Morbidity and Mortality Weekly Report

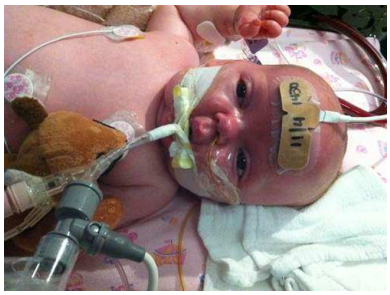
Updated Recommendations for Use of Meningococcal Conjugate Vaccines — Advisory Committee on Immunization Practices (ACIP), 2010

Booster dose
At age 16 years if primary dose at age 11 or 12 years
At age 16 through 18 years if primary dose at age 13 through 15 years
No booster needed if primary dose on or after age 16 years

MMWR / January 28, 2011 / Vol. 60 / No. 3

Essential contribution of epidemiology

ANALYSIS OF OUTBREAKS



Whole cell pertussis vaccine was used until 1997 when acellular pertussis vaccine was licensed

Acellular pertussis vaccine was licensed and recommended for 11 and 12 year olds in 2005

The New York Times

Whooping Cough Kills 5 in California; State Declares an Epidemic

By JESSE McKINLEY
Published: June 23, 2010

SAN FRANCISCO — After the deaths of five infants, California health authorities declared an epidemic of whooping cough in the state on Wednesday, urging residents — particularly those of Latino background — to get vaccinated against the disease.

RECOMMEND
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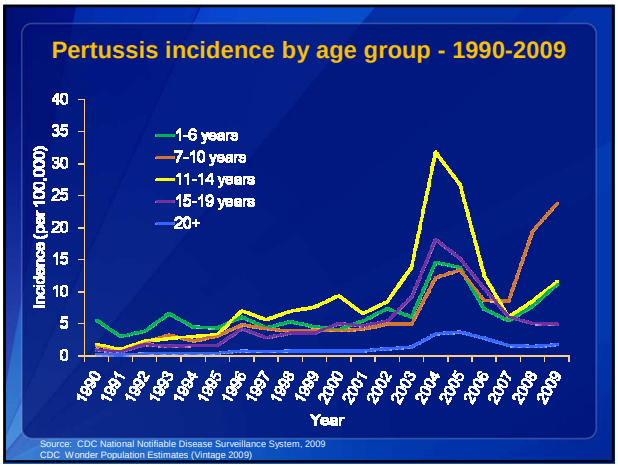
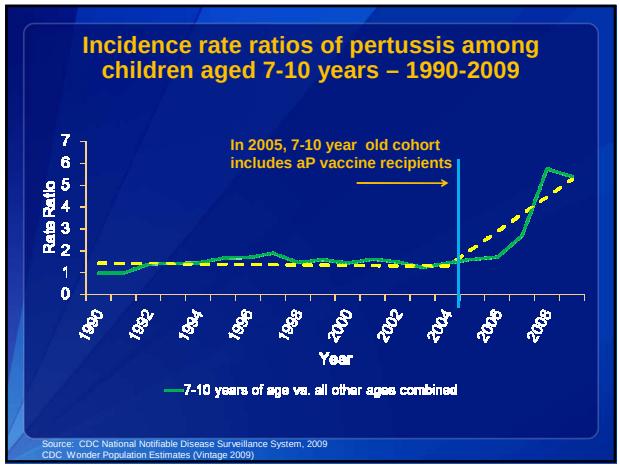
LINKEDIN
SIGN IN TO E-





Morbidity and Mortality Weekly Report

Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine from the Advisory Committee on Immunization Practices, 2010

Children Aged 7 Through 10 Years

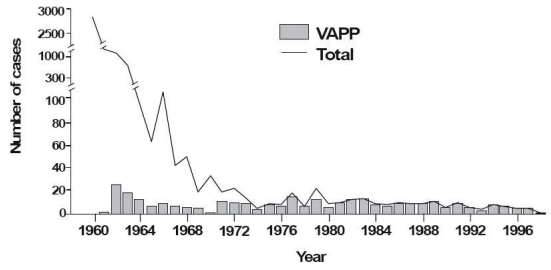
- Those not fully vaccinated against pertussis* and for whom no contraindication to pertussis vaccine exists should receive a single dose of Tdap.
- Those never vaccinated against tetanus, diphtheria, or pertussis or who have unknown vaccination status should receive a series of three vaccinations containing tetanus and diphtheria toxoids. The first of these three doses should be Tdap.

* Fully vaccinated is defined as 5 doses of DTaP or 4 doses of DTaP if the fourth dose was administered on or after the fourth birthday.

Two significant examples: OPV to IPV and DTP to DTaP

CHANGING TO A SAFER VACCINE

FIGURE. Total number of reported paralytic poliomyelitis cases and total number of reported vaccine-associated paralytic polio (VAPP) cases — United States, 1960–1998*



*Updated June 16, 1999.

TABLE 2. Percent of vaccinated children seropositive* following vaccination with IPV† alone, OPV§ alone or IPV followed by OPV: Studies conducted in the United States

Studies	Vaccine schedule Type of vaccine administered 2 mos.	4 mos.	6 mos.	12–18 mos.	N¶	Poliovirus serotype After dose 2 P1	P2	P3	After dose 3 P1	P2	P3	After dose 4 P1	P2	P3
McBean et al. [32]	I** †	I		I	331	99	99	99	99	100	100			
	I	I		I	332	99	100	100	100	100	100			
	O§	O		O	337	92	100	96	97	100	100			
Faden et al. [36]	I**	I		I	91	96	100	96	96	100	100			
	O	O		O	22	100	100	100	100	100	100			
	I**	O		O	29	94	100	94	100	100	100			
	I**	I		O	29	100	100	100	100	100	100			
Modlin et al. [37]	I§§	I		I	101	97	92	78	100	100	100			
	O	O		O	98	95	100	90	95	100	100			
	I§§	I		O	98	90	93	74	97	100	85			
	I§§	I	O	O	106	89	96	71	94	100	81	95	100	95
	I§§	I/O	O	O	101	96	100	85¶¶	93	99	97***	98	100	100†††
Blatter & Starr [46]	I**	I		I	94	97	96	95	100	100	100			
	I††	I		I	68	98	100	98	100	100	100			
	I**	I		O	75	94	98	96	100	100	96			
	I††	I		O	99	99	99	95	100	100	99			
Halsey et al. [45]	I††	I	I	O	97	98	98	100	100	100	100	100	100	100
	I††	I	O	O	96	100	97	99	100	100	100	100	100	100
	I††	I	I/O	O	91	95	96	100	100	100	100***	100	100	100†††

TABLE 3. Advantages and disadvantages of three poliovirus vaccination options

Attribute	OPV*	IPV†	IPV-OPV§
Occurrence of VAPP¶	8–9 cases/year	None	2–5 cases/year**
Other serious adverse events	None known	None known	None known
Systemic immunity	High	High	High
Immunity of GI mucosa	High	Low	High
Secondary transmission of vaccine virus	Yes	No	Some
Extra injections or visits needed	No	Yes	Yes
Compliance with immunization schedule	High	Possibly reduced	Possibly reduced
Future combination vaccines	Unlikely	Likely	Likely (IPV)
Current cost	Low	Higher	Intermediate

*Oral poliovirus vaccine.
†Inactivated poliovirus vaccine.
§Sequential vaccination with IPV and OPV.
¶Vaccine-associated paralytic poliomyelitis.
**Estimated.

CDC
January 24, 1997 / Vol. 46 / No. RR-3
MMWR
Recommendations and Reports
MORBIDITY AND MORTALITY WEEKLY REPORT

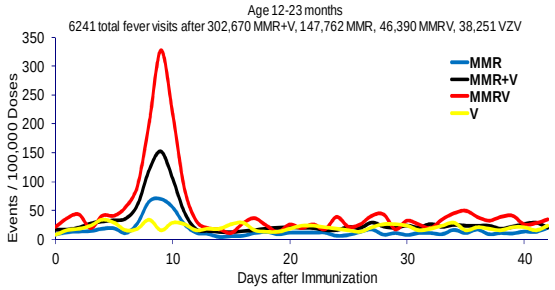
Poliomyelitis Prevention in the United States: Introduction of a Sequential Vaccination Schedule of Inactivated Poliovirus Vaccine Followed by Oral Poliovirus Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

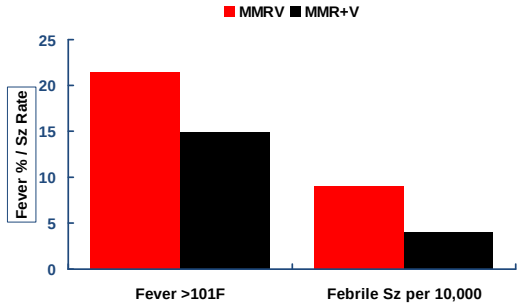
Essential to maintain safety of and confidence in the program

NEW SAFETY SIGNAL

Outpatient Visits for Fever by Day after Vaccine at Northern California Kaiser Permanente: 1995-2008



Adverse Reactions Following MMRV or MMR+V



Shinefield et al, PIDJ 2005; CDC unpublished data 2008

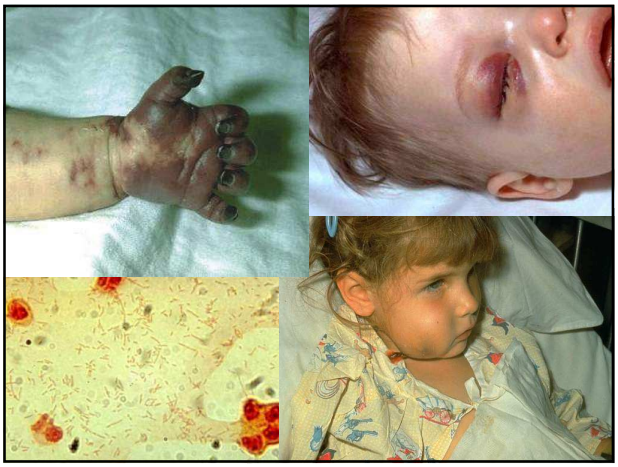
WR March 14, 2008

Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine

On February 27, 2008, new information was presented to the Advisory Committee on Immunization Practices (ACIP) regarding the risk for febrile seizures among children aged 12–23 months after administration of the combination measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad®, Merck & Co., Inc., Whitehouse Station, New Jersey). This report summarizes current knowl-

Temporary recommendations made by CDC in consultation with ACIP

VACCINE SHORTAGE



Interim Recommendations for the Use of *Haemophilus influenzae* Type b (Hib) Conjugate Vaccines Related to the Recall of Certain Lots of Hib-Containing Vaccines (PedvaxHIB® and Comvax®)

On December 19, this report was posted as an MMWR Dispatch *on the* MMWR *website* (http://www.cdc.gov/mmwr).

On December 13, 2007, Merck & Co., Inc. (West Point, Pennsylvania) announced a voluntary recall of certain lots of two *Haemophilus influenzae* type b (Hib) conjugate vaccines, PedvaxHIB® (monovalent Hib vaccine) and Comvax® (Hib/hepatitis B vaccine). Providers should return unused vaccine from these recalled lots using procedures outlined

CDC. MMWR 2007; 56(50):1318-1320

Invasive *Haemophilus influenzae* Type B Disease in Five Young Children — Minnesota, 2008

On January 23, this report was posted as an MMWR Early Release *on the* MMWR *website* (http://www.cdc.gov/mmwr).

Vol. 58 / No. 3 MMWR 59

TABLE. Characteristics of five reported cases of invasive *Haemophilus influenzae* type b (Hib) disease* in persons aged <5 years — Minnesota, 2008

Patient	Month of illness onset	Patient age at illness onset	Clinical syndrome†	Outcome	Hib vaccination status
1	January	15 mos	Meningitis	Survived	2 doses at 2 and 5 months (PRP-OMP)§
2	February	3 yrs	Pneumonia	Survived	0 doses
3	November	7 mos	Meningitis	Died	0 doses
4	November	5 mos	Meningitis	Survived	2 doses at 2 and 4 months (PRP-TT)¶
5	December	20 mos	Epiglottitis	Survived	0 doses

* Defined as isolation of *H. influenzae* from a normally sterile site in a Minnesota resident.
† One patient had meningitis with subdural abscess.
§ Hib vaccine, capsular polysaccharide polyribosomal phosphate (PRP)–outer membrane protein (OMP), 2-dose primary series.
¶ Hib vaccine, PRP-tetanus toxoid, 3-dose primary series.

CDC MMWR 2009; 58(3):58-60

Automatically provides money to purchase the vaccine

ADDING A VACCINE TO VFC

Resolution No. 010/11-1

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

VACCINES FOR CHILDREN PROGRAM

VACCINES TO PREVENT HUMAN PAPILLOMAVIRUS

The purpose of this resolution is to: allow routine use and catch up of the quadrivalent HPV vaccine for VFC-eligible males, 9 through 18 years old, and to streamline the resolution through the use of links to published documents.

VFC Resolution 10/09-1 is repealed and replaced by the following:

Eligible Groups

Gender and Age	Bivalent HPV vaccine	Quadrivalent HPV vaccine
Females, 9 through 18 years	Eligible	Eligible
Males, 9 through 18 years	Not eligible	Eligible

Many adjustments were made for measles

POLICY CHANGES OVER DECADES

U.S. Measles Vaccination Policy
美国麻疹疫苗接种策略

Year	Dose 1 age	Dose 2 age	Reason for change
1963	**9** months	--	Vaccine licensed 疫苗注册
1965	**12** months	--	Persistent maternal antibody持续的母传抗体 High vaccine failure rate at 9 months在9月龄接种高疫苗失败率
1976	**15** months	--	High vaccine failure rate at 12 months 12月龄时接种高疫苗失败率
1989	**15** months	**4 - 6** years	School outbreaks showed need for 2 doses 学校暴发提示需要2剂次
1990s	**12 - 15** months	**4 - 6** years	Desire for earlier protection希望早期保护 Catch-up vaccination for second dose第二剂次初始活动
2000	**12 – 15** months	**4 – 6** years	Measles elimination certified 证实消除麻疹

STRENGTHS, WEAKNESSES, AND CHALLENGES

Strengths

- Evidence based
- Publicly and transparently made
- CDC controls ACIP agenda
- Authorized by law to mandate payment for vaccines in private and public sector

Weaknesses

- Federal government does not specify which vaccines should be made
  - Manufacturers decide what vaccines to make
  - The new National Vaccine Plan specifies a process to indicate vaccines to make
- CDC is not in a strong position to negotiate vaccine prices for public sector entitlement

Challenges

- Establishing surveillance system for newly vaccine preventable diseases is costly and does not have an automatic budget
- No automatic budget for promotion of new vaccine recommendation

Conclusions (1)

- U.S. immunization policy is supported by laws that bind CDC/ACIP recommendations to standards of medical care and immunization financing
- ACIP is the focal point of U.S. immunization policy, but ACIP working groups led by CDC scientists generate evidence and guide the ACIP process
- Generating new knowledge and evidence is a responsibility of CDC and requires substantial resources, both personnel and financial

Conclusions (2)

- CDC controls the ACIP agenda, which assures that ACIP works on the most important immunization issues
- ACIP meetings are public and broadcast on the Internet, providing a level of transparency that helps the public understand the rationale for immunization policy decisions
- What this talk did not cover: program implementation
  - (1) Communication, (2) measuring coverage; (3) research on barriers to immunization; (4) assuring vaccine supply; (5) vaccine ordering and distribution; (6) training and education; (7) Information Technology infrastructure; (8) technical assistance for states; (9) partnerships

Conclusions (3)

I am thrilled to be in China

I am looking forward to working together with you, as you help China's children stay healthy and happy

THANK YOU!

EXTRA SLIDES

TABLE. Summary results from Vaccine Safety Datalink (VSD) and Merck-sponsored studies for febrile seizure after the first dose of measles, mumps, rubella and varicella vaccine (MMRV) compared with the first dose of measles, mumps, rubella vaccine (MMR) and varicella vaccine (V) administered at the same visit — United States, 2009

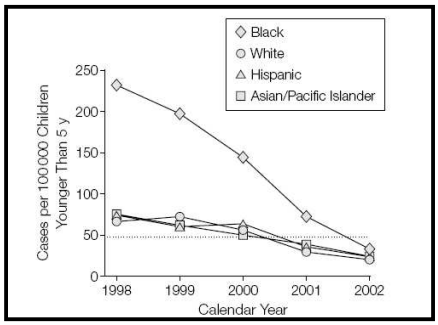
Characteristic	VSD*	Merck-sponsored†
Age/No. subjects, by vaccine	All aged 12–23 months MMRV: n = 83,107 MMR and V: n= 376,354	99% aged 12–23 months MMRV: n = 31,298 MMR and V: n = 31,298
Postvaccination interval		
Week 1–2	7–10 days§ RR: 2.0 (CI = 1.4–2.9) AR: 4.3 per 10,000 (CI = 2.6–5.6)	5–12 days§ RR: 2.2 (CI = 1.0–4.7) AR: 3.8 per 10,000 (CI = 0.3–7.4)
Week 1–6	0–42 days§ RR: 1.5 (CI = 1.1–1.9) AR: 6.2 per 10,000 (CI = 2.0–9.5)	0–30 days RR: 1.1 (CI = 0.7–1.7) AR: 1.3 per 10,000 (CI = -4.5–7.0)

RR = relative risk; AR = attributable risk; CI = 95% confidence interval.
* **Source:** Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010. In press.
† **Source:** Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009;27:4656–61.
§ Statistically significant at <0.05.

Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine
Recommendations of the Advisory Committee on Immunization Practices

MMWR Morbidity and Mortality Weekly Report

Impact of PCV7 Vaccine on Racial Disparities in Invasive Strep pneumoniae Infection



Flannery et al. *JAMA* 2004; 291: 2197 - 2203

TABLE 1. Summary of recommendations of the Advisory Committee on Immunization Practices (ACIP) for prevention of varicella — United States, 1996, 1999, and 2007

Category	1996 recommendations	1999 recommendations	2007 recommendations
Routine childhood schedules	1 dose recommended at age 12–18 months	No change	2 doses recommended • 1st dose at age 12–15 months • 2nd dose at age 4–6 years