What Immunization Providers Need to Know about Vaccine Safety and Addressing Parental Concerns

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Overview of Presentation

- How we assess vaccine safety in the United States
- Updates on several current vaccine safety issues
- What are parents concerned about, and how to address those concerns

Disclosure

- No financial relationships to disclose
- No discussion of investigational products or recommendations for off-label use of licensed vaccines

What Immunization Providers Need to Know

HOW WE ASSESS VACCINE SAFETY IN THE UNITED STATES

The Vaccine Safety System

- **When the vaccine is under development, studies are done to find out if it is safe and effective**
- **FDA review: if safe and effective, vaccine can be licensed**
  - Other issues (manufacturing etc.) also considered by FDA
- **Ongoing monitoring by both CDC and FDA and by the manufacturer after licensure**
  - Post-licensure studies by the manufacturer
  - Vaccine Adverse Event Reporting System (VAERS)
  - Special studies
- **If vaccine safety issues are identified, actions are taken**

Vaccine Safety

- **Surveillance**
  - Vaccine Adverse Event Reporting System
- **Rapid studies**
  - Rapid cycle analysis through the Vaccine Safety Datalink
- **Other special studies**
  - Guillain-Barré syndrome following H1N1 vaccine
  - Vaccines and autism
- **Prevention**
  - Contraindications and precautions for use of vaccines
  - Withdrawal of recommendations for use of vaccines

Vaccine Adverse Event Reporting System

- **National spontaneous reporting system for adverse events following immunization**
- **Jointly run by CDC and FDA**
- **VAERS has led to early identification of serious adverse events**
- **Limitations**
  - Reporting is not complete
  - Rarely able to establish a causal relationship to vaccine based on reports to VAERS
- **VAERS reports can be submitted online and data are publicly accessible: http://vaers.hhs.gov**

A Faster Approach to Vaccine Safety Studies

- **Alternative to traditional post-licensure vaccine safety study methods, which generally take years to complete**
- **The Rapid Cycle Analysis approach in the Vaccine Safety Datalink:**
  - Tests specific hypotheses with well-defined outcomes
  - Each week, evaluate the number of events in vaccinated persons
  - Compare it to the expected number of events based on a comparison group
  - Weekly analyses with statistical adjustment for multiple looks
- **Rapid Cycle Analyses have:**
  - Provided reassuring data on safety of several newly introduced vaccines (e.g., Rotateq, 2009 H1N1 vaccine)
  - Identified increased risk of febrile seizures following MMRV vaccine

Lieu TA, et al. Real-time vaccine safety surveillance for the early detection of adverse events. Med Care. 2007 Oct;45:S89-95.

Are Vaccines Safe?

- **Minor adverse events are common**
- **Serious adverse events that we know are caused by vaccines are not common**
  - Oral polio vaccine caused vaccine-associated polio in 1 out of 750,000 first doses
  - Influenza vaccine caused Guillain-Barré syndrome in 1 out of 100,000 doses (1976)
  - MMR causes thrombocytopenia in 1 out of 30,000 doses

Not Everything Bad that Happens after Vaccination is *Caused* by the Vaccine

- **Most of the conditions that people worry about vaccines causing occur unrelated to vaccination**
  - Guillain-Barré syndrome occurs unrelated to immunization with about 1 case per year in 100,000 people
- **Except for the disease the vaccine prevents, all of the health outcomes – including deaths – that happen to people anyway keep happening after vaccination**

How Do We Decide if an Adverse Event is Caused by a Vaccine?

- Live virus vaccine strains can be isolated and distinguished by molecular techniques from "wild type" strains
- Comparing the frequency that an adverse event occurs in a time interval after vaccination with the frequency that an adverse event occurs in a time interval that is not after vaccination

How Do We Decide What We Are Going to Worry About?

- **Consistent pattern of clinical findings**
- **Biologic plausibility**
- **Consistency of findings in other studies**
- **Clustering of cases in time after vaccination, especially in a "biologically plausible" interval**
- **Observed cases > expected cases**
  - Calculations require knowing what the incidence of the condition is, and how many doses of vaccine have been given

What Do We Do When We Find Something?

- **Communicate the finding to immunization providers and to the public**
- **Begin a field investigation or a research study**
  - Can the adverse event be prevented?
  - Who is at increased risk for the adverse event?
- **Reconsider risks and benefits of the vaccine**

Vaccine Safety: A Shared Responsibility

- **Immunization providers:** safe storage & handling, safe immunization practices, communicating risks and benefits, reporting of adverse events
- **Parents:** tell your doctor about allergies and previous adverse reactions, ask questions and get the information you need

What Immunization Providers Need to Know

UPDATE ON VACCINE SAFETY

Safety and Efficacy Issues Potentially Associated with the Childhood Vaccination Schedule

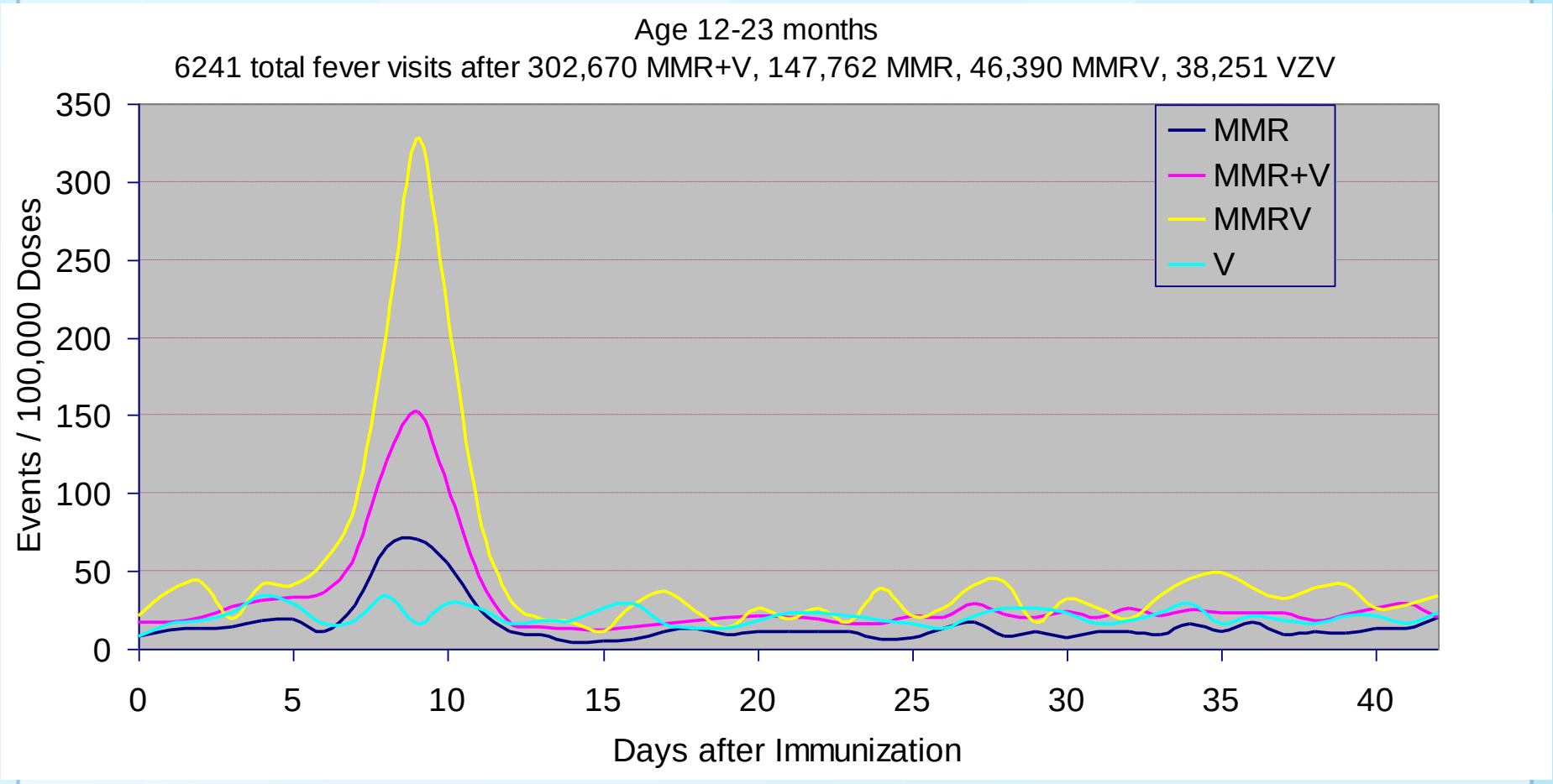
- Data generally available on concurrent administration at licensure
- Interference between concurrently administered vaccines theoretically possible but generally not observed
  - Need for spacing of live virus vaccines
- Safety or efficacy issues associated with concurrent or antecedent exposure to vaccine components (e.g., diphtheria toxoid-containing vaccines)
- Cumulative exposure to vaccine components

Data on Simultaneous Administration for a Licensed Vaccine: ROTARIX

- 484 healthy infants randomized into two groups
- All received Pediarix, PCV7, and ActHib at 2, 4, and 6 months and either ROTARIX concurrently at 2 and 4 months or separately at 3 and 5 months
  - Co-administration: n=249
  - Separate administration: n=235
- Prespecified criteria for noninferiority of antibody response met for all antigens

Abu-Elyazeed et al, ICAAC 2007

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

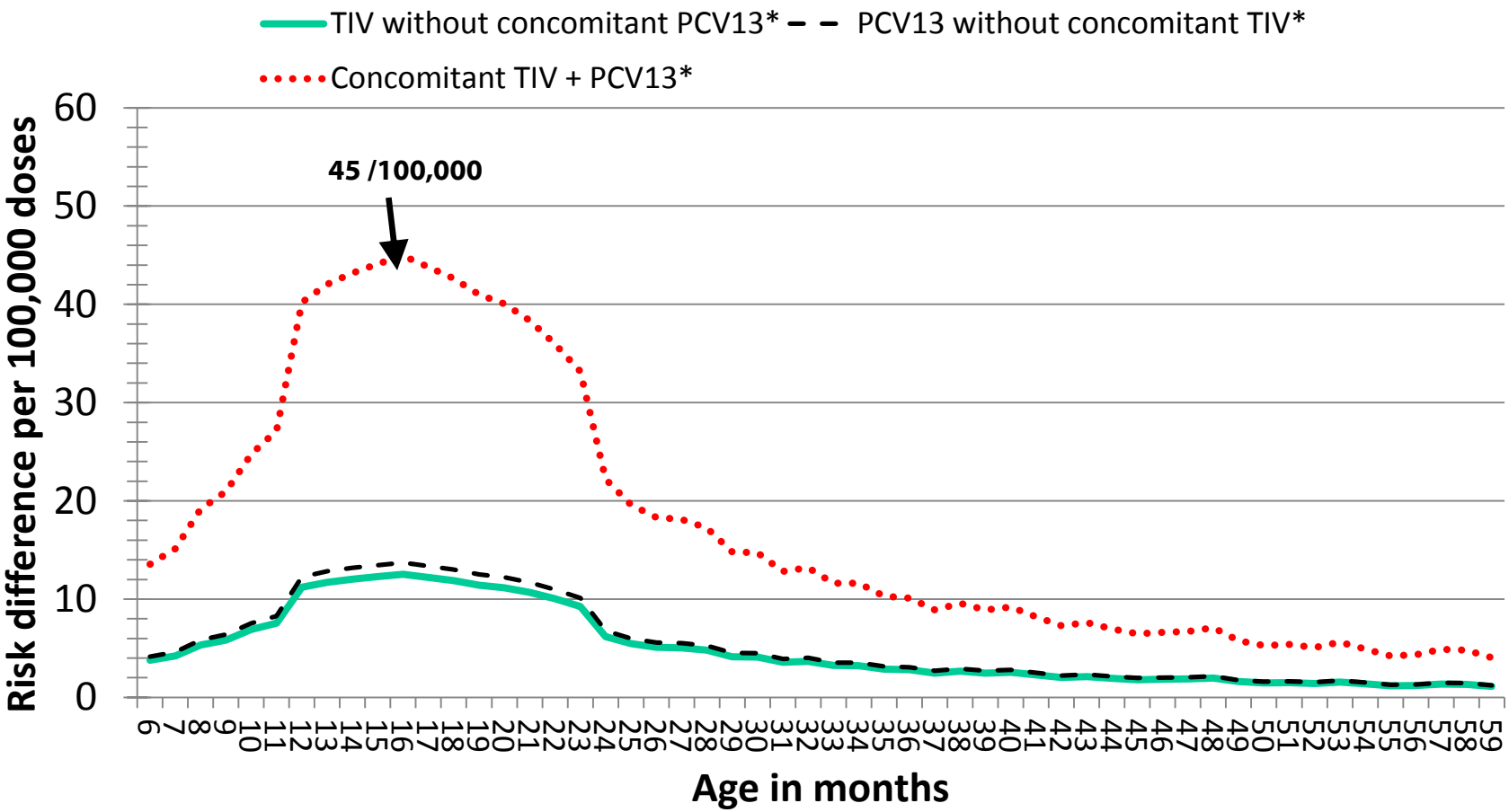


Vaccine Safety Datalink; Immunization Safety Office, CDC

Febrile Seizures following MMRV

- **In 2008 Rapid Cycle Analysis safety monitoring detected an increase in febrile seizures following MMRV**
- **MMRV was associated with a 2-fold increase in risk of fever and febrile seizures 7-10 days after MMRV compared with separately administered MMR+V among 12-23 month olds.**
  - CDC recommended MMR+V unless parent/guardian prefers MMRV
- **No increase in risk found for MMRV compared with MMR+V among 4-6 year olds.**

Risk Difference (Excess Risk) Estimates for Febrile Seizures following 1st Dose TIV, 2010-11†



†Tse A and Lee G for the VSD

*Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines

TIV, PCV13, and Febrile Seizures

- Timely influenza and pneumococcal vaccination may prevent febrile seizures by protecting young children against influenza and pneumococcal infections, both of which can cause fever
- Clinical studies have not shown that fever-reducing medicines (e.g., acetaminophen, ibuprofen) prevent febrile seizures
- Aspirin and aspirin-containing products should not be used to reduce fever in children because of the increased risk for Reye syndrome with aspirin ingestion and viral infections
- Further investigation is underway to determine if other childhood vaccines besides TIV and PCV13 may be contributing to the febrile seizures

Rotavirus Vaccines and Intussusception

- A very high risk (>30-fold) of intussusception in the first week following dose 1 of an earlier rotavirus vaccine led to its withdrawal in 1999
- Large prelicensure studies performed for both RotaTeq and Rotarix
- An elevated risk of intussusception following dose 1 found in postlicensure studies in Australia (RotaTeq) and Mexico (Rotarix) but not in Brazil (Rotarix)
- A postlicensure study of RotaTeq in the U.S. in the Vaccine Safety Datalink found no increase risk

Syncope (Fainting) following HPV Vaccine

- Increased reporting of syncope among vaccinees
- Although usually not serious, syncope can result in falls, which sometimes cause serious injuries, especially head injuries
- Syncope recognized to occur following vaccination, especially among adolescents and adults

VAERS "Serious" Reports of Syncope following HPV Vaccine

- **Total number of serious reports: 202**
- **Injuries resulting from syncopal event:**
  - Fractures (nose, skull, maxillary)
  - Dental injuries
  - Contusions
  - Concussions
  - Intracranial hemorrhages (subdural hematoma, subarachnoid hemorrhage)
- **No reports of death resulting from injury following a vasovagal syncopal event**

General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

"…, although syncopal episodes are uncommon … vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until symptoms resolve."

MMWR 2006; 55 (No. RR-15)

Verified VAERS Reports of Death following HPV Vaccine

- **Reported causes of death after clinical review with median onset interval:**
  - Neurological: 7 (Seizures 5, ALS 2); 53 days (13-745)
  - Cardiac: 7 (Arrhythmia 3, myocarditis 3, congenital); 9 days (2-25)
  - Pulmonary embolism: 4; 14.5 days (13-181)
  - Infectious: 5 (Group A strep 2, *N. meningitidis*, MRSA, HIV-CNS vasculitis); 29 days (4-117)
  - Other, noninfectious: 4 (suicide; type 1 DM DKA; drug overdose; dermatomyositis) 35 days (2-594)
  - Undetermined cause of death: 7; 17 days (2-121)
- **No patterns in verified death reports**

HPV4 Rapid Cycle Analysis Results: Vaccine Safety Datalink

- **VSD active surveillance confirmed no significant risk for any of the pre-specified adverse events after vaccination**
  - GBS, seizures, syncope, appendicitis, stroke, VTE, and other allergic reactions
  - Additional study is needed for a possible non-statistical association between HPV4 and VTE
    - All confirmed cases had other risk factors for VTE
- **No increase in rate of anaphylaxis following HPV4 as compared to previous VSD studies**

HPV Vaccine Safety: Summary

- **No new adverse event concerns or clinical patterns identified in VAERS review**
- **VSD rapid cycle analysis confirmed no significant risk for pre-specified adverse events* after vaccination for females 9-17years and 18-26 years**
  - GBS, seizures, syncope, appendicitis, stroke, venous thromboembolism (VTE), and other allergic reactions
  - Non-statistically significant increased relative risk of VTE among 9-17 year olds
- **Further evaluation of VTE post-vaccination ongoing**
- **Long-term follow-up of adolescents have not identified any safety concerns**

Wrong Drug Administered
Mix-ups for 100 Random Reports

- **The most frequent vaccine combinations mix-ups from a random sample of wrong drug administered reports:**
  - Varicella-Zostavax mix-ups 25% (n=25) where:
    - Varicella given instead of Zostavax(16) Zostavax given instead of Varicella (9)
  - DTaP-Tdap mixups 11% (n=11)
    - DTaP given instead of Tdap (8) Tdap given instead of DTaP (3)
  - Pneumovax-Prevnar mix-ups 7% (n=7)
    - Pneumovax given instead of Prevnar(6), Prevnar given instead of Pneumovax (2)
- **10 (10%) reports also reported an adverse health event; two serious report (meningitis, otitis media/influenza).**
  - Adverse health events among non-serious reports: Injection site reaction (3) Fever (2) Respiratory (1), Constitutional symptoms (1), Allergic (1)

Eye Splashes and Rotavirus Vaccines

- **25 reports from 2006-2011* of an eye splash following administration of rotavirus vaccines.**
- **80% (20) reports involved an infant coughing, sneezing or spitting the vaccine into eyes.**
  - Eye splash by other means (4) and unknown exposure route (1).
- **Persons Affected by Eye Splash: 80% Health Care Providers, Patients 12% , Parents 8% .**
- **Adverse health event affecting the eye were reported in 64% (16) eye splash reports.**
  - All 16 reports that described an eye adverse event occurred in Health Care Providers and were non serious.

*Rotavirus vaccine was licensed in 2006. Error codes for accidental exposure and Grouped Eye MedDRA codes used in VAERS data analysis

Role of Clinicians in Preventing Vaccine Administration Errors

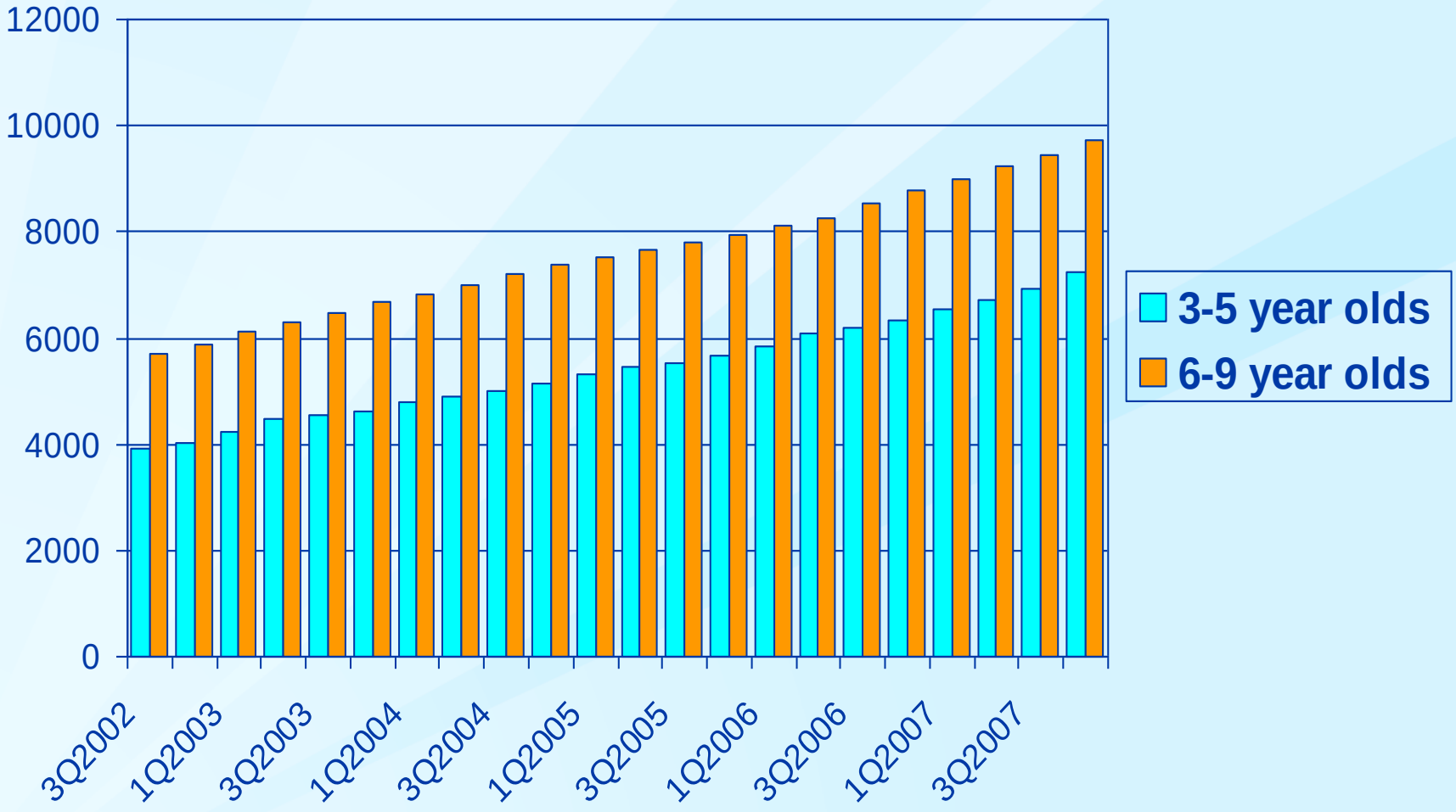
- **Proper Storage and Handling of Vaccines**
  - Vaccine Storage and Handling Guide (tool kit under revision), Pink Book Chapter 5, www.cdc.gov
  - http://www.cdc.gov/vaccines/recs/storage/default.htm
- **Identify Contraindications & Precautions**
  - Immunization Screening Questionnaires, www.cdc.gov
- **Proper Vaccine Administration -Right patient, Right time , Right dose, Right route, Right drug***
  - General Recommendations on Immunization www.cdc.gov
  - http://www.cdc.gov/vaccines/recs/vac-admin/default.htm
- **Report Clinically Significant Vaccination Errors to VAERS**
  - VAERS www.vaers.hhs.gov

*The five "rights" of medication administration

Thimerosal and Autism: What Does the Science Show?

- Ecologic studies: autism does not go down when thimerosal is removed from childhood vaccines
- Epidemiologic studies: well-designed studies demonstrate no association between thimerosal exposure from vaccines and autism
- Biochemical studies and animal models interesting but uninformative

Children Receiving Autism Services by Quarter, California, 2002-2007



California Department of Developmental Services

Vaccines and Autism, Still

- MMR and autism (1998)
- Thimerosal and autism (2001)
- Simultaneous administration of multiple vaccines and the "one size fits all" immunization schedule (2007)
- Mitochondrial disorders (2008)

Vaccines and Autism: Context

- Heuristics and biases
- Distrust of government
- Unanswered questions about autism and real needs of families
- Advocacy
- Litigation
- Modern social networking tools

"Why doesn't CDC study autism rates in unvaccinated children?"

- **Almost all children in the U.S. have received at least some vaccines; less than 1% of children have received no vaccines**
- **Although recognized autism spectrum disorders more common than previously reported (up to 1 in 88 children), disease is infrequent enough that a large population needed to identify sufficient cases for a study**
- **Unvaccinated children probably very different from other children in terms of:**
  - Healthcare utilization
  - Other exposures

Filling in Knowledge Gaps

- **Concerns about whole cell pertussis vaccine (DTP) and encephalopathy**
- **Dravet syndrome**
  - Severe disease with hard-to-control seizures, progressive course, poor prognosis
  - Many cases are associated with de novo mutations in a specific gene
- **A recent study suggests that many cases of encephalopathy after DTP are Dravet syndrome**

Berkovic, Lancet Neurology 2006

SMEI and "Vaccine Encephalopathy"

- **Epileptic encephalopathies, without other specific cause identified, with first seizure onset within 72 hours of vaccination**
- **Cases ascertained by child neurologists in Australia and New Zealand 2002-2003**
- **Diagnoses:**
  - SMEI – 8 patients
  - SMEB – 4 patients
  - Lennox-Gastaut syndrome – 2 patients
- **Molecular analysis:**
  - Heterozygous mutations of *SCN1A* in 11 of 14 cases

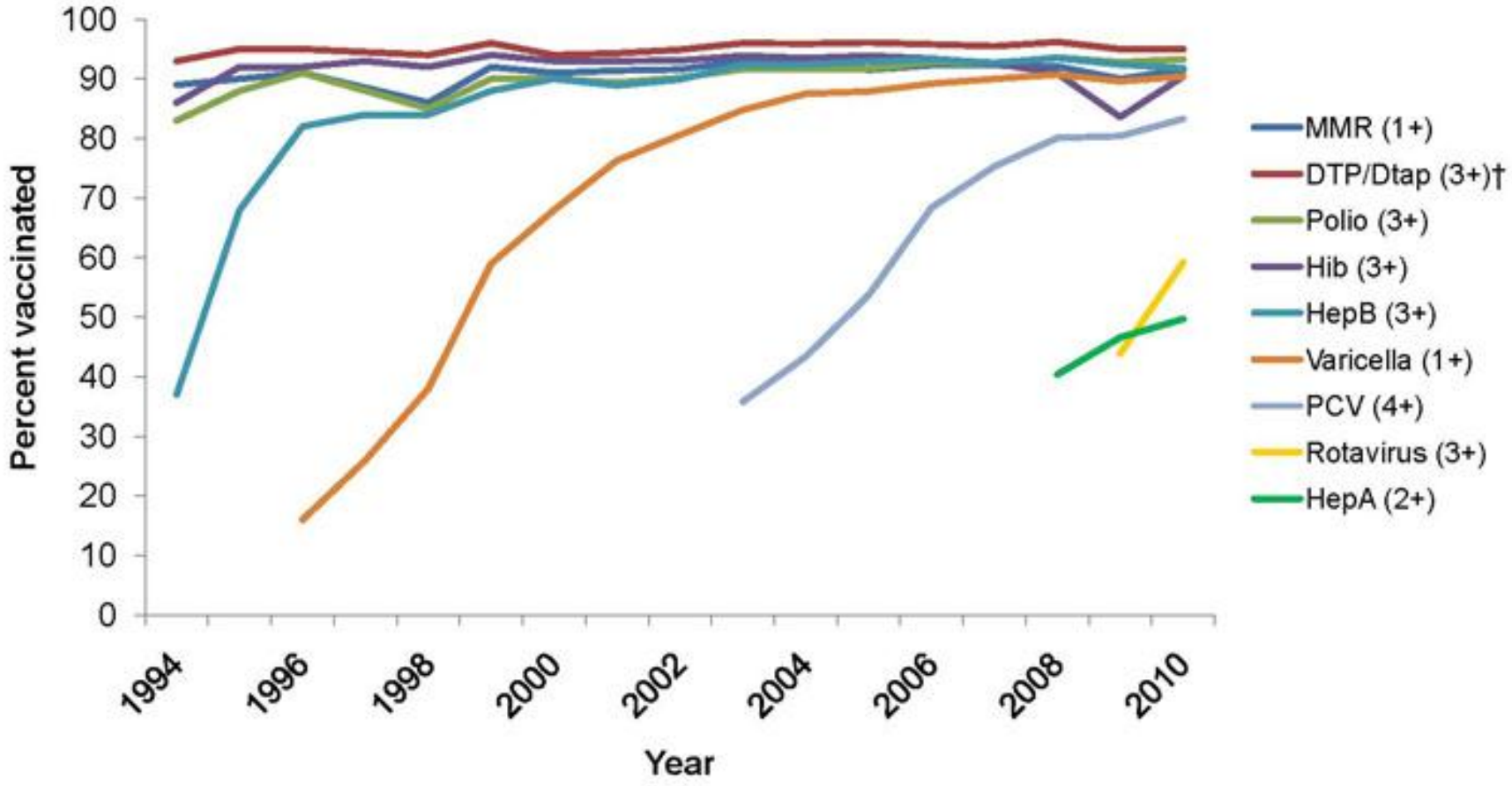
Berkovic, Lancet Neurology 2006

What Immunization Providers Need to Know

ADDRESSING PARENTAL CONCERNS

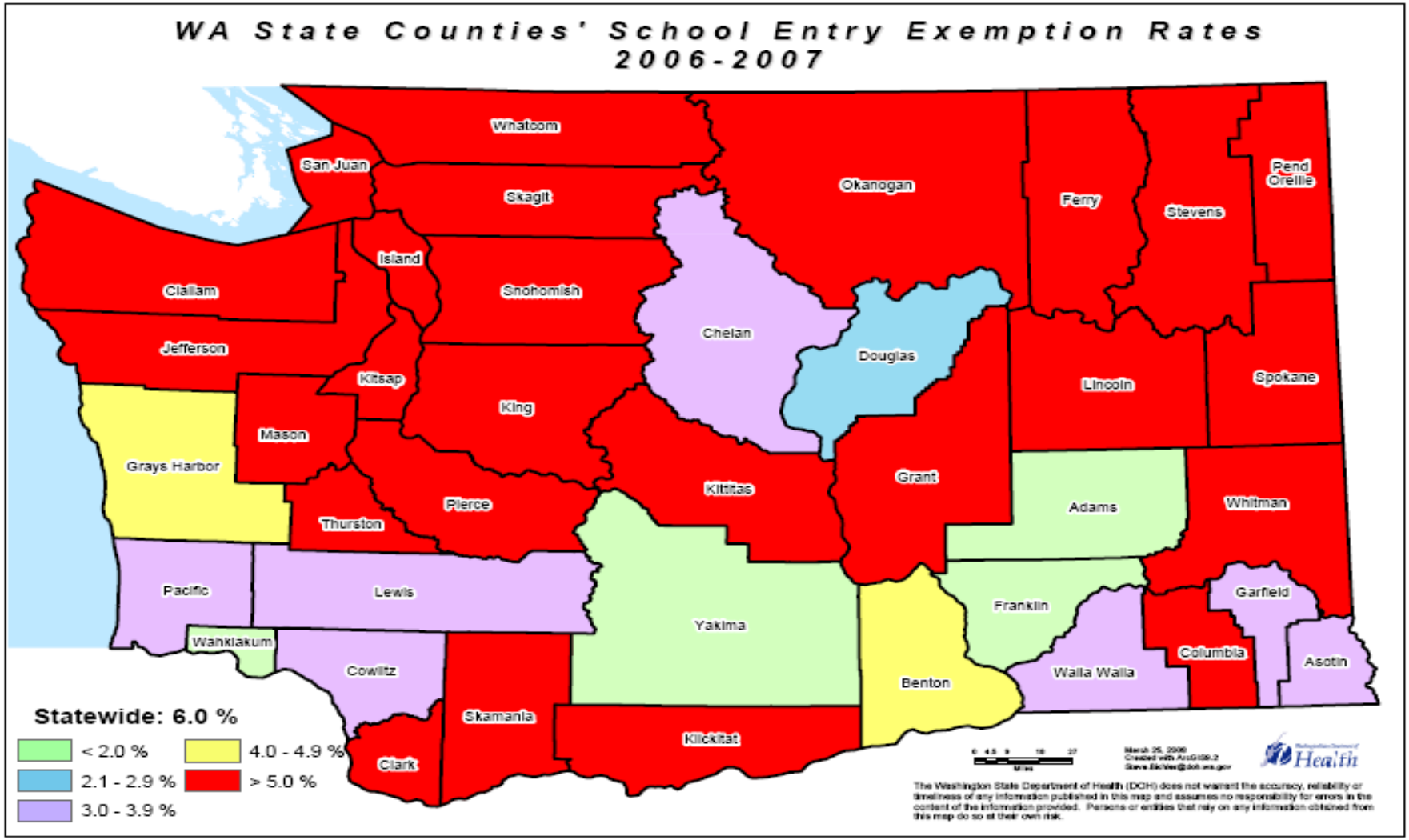

MACLEAN'S
AUG. 27th 2007
BARBARA AMIEL: I'm home alone P.12
OUR GIRLS AREN'T GUINEA PIGS
A mass inoculation of Canadian girls against a sexually transmitted virus is under way. Experts say it's unnecessary—and potentially dangerous.

Vaccine-specific coverage* among children 19-35 months, National Immunization Survey, 1994-2010



* The Healthy People 2020 target for coverage is 90% for all vaccines with the exception of rotavirus (80%) and HepA (60%).

† DTP (3+) is not a Healthy People 2020 objective. DTaP (4+) is used to assess Healthy People 2020 objectives.



Data source: Washington State DOH Immunization Program CHILD Profile

Invasive *H. influenzae* type B disease -- Minnesota, 2008

- **5 cases of invasive Hib disease in children <5 years of age; 1 death**
- **Geographically dispersed and not epidemiologically linked**
- **None of the children had been fully vaccinated against Hib**
  - 3 children had received no vaccinations because of parental refusal
  - 2 were partially vaccinated
- **Occurred during national shortage of Hib vaccine that began in December 2007**

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58e0123a1.htm

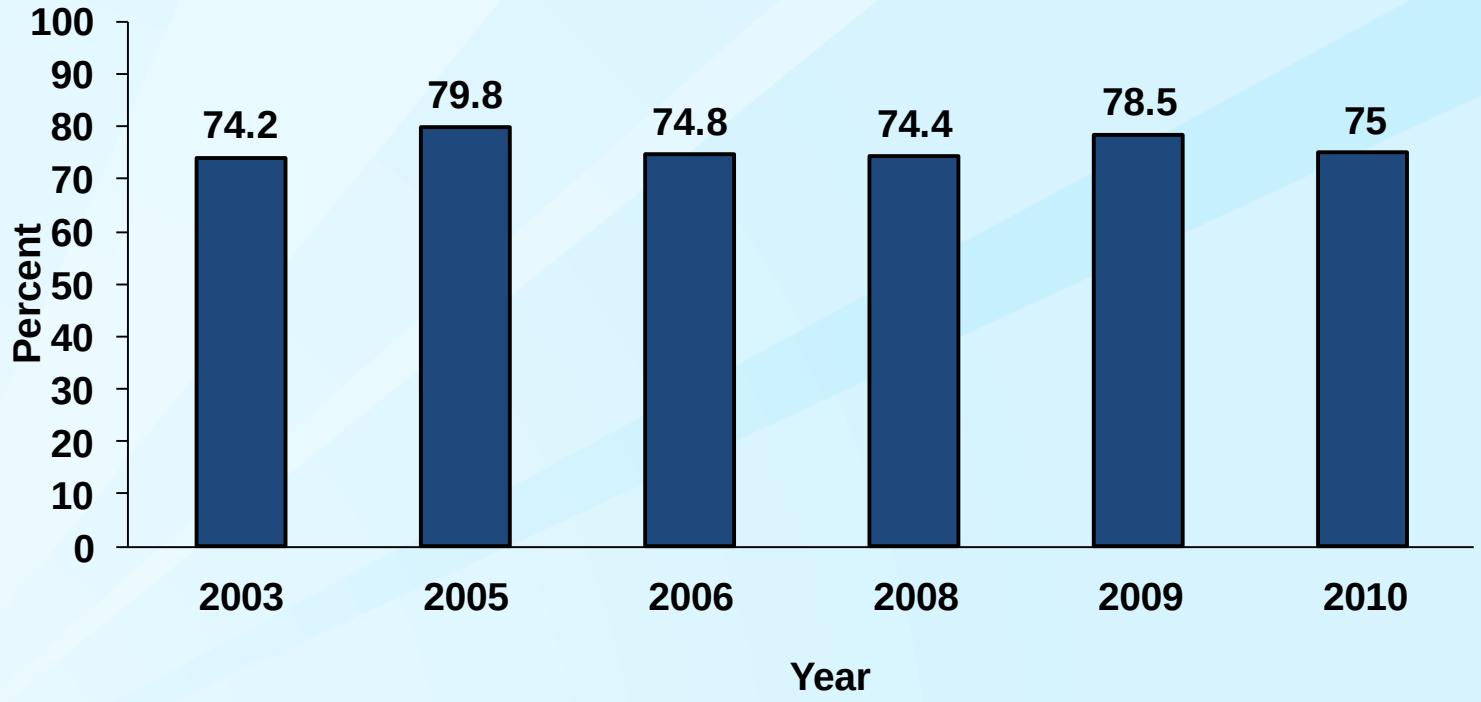
What Parents are Concerned About (2010)

- It is painful for children to receive so many shots during one doctor's visit (38%)
- My child is getting too many vaccines in one doctor's visit (36%)
- Children get too many vaccines during the first two years of life (34%)
- Vaccines may cause learning disabilities, such as autism (30%)
- The ingredients in vaccines are unsafe (26%)
- Vaccines are not tested enough for safety (17%)
- Vaccines may cause chronic disease (16%)

Kennedy A et al, Health Affairs 2011;30:1151-1159

Confidence in Vaccine Safety

Percent of parents who reported that they were confident or very confident in the safety of routine childhood vaccines



Source: PN Healthstyles

"What are the three most important sources of information that have helped you make decisions about your youngest child's vaccinations?"

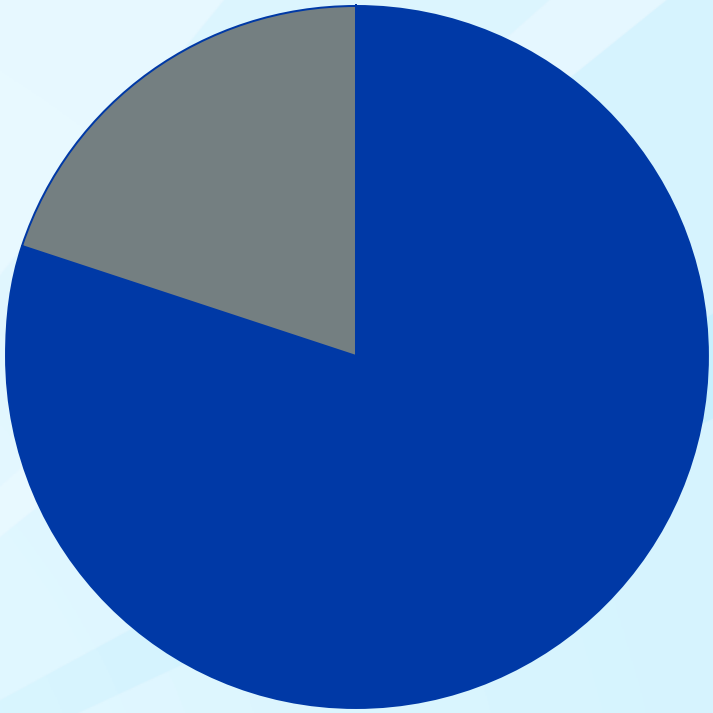
- Child's health care provider (68.3%)
- Family (45.4%)
- Child's other parent (22.7%)
- American Academy of Pediatrics (21.8%)
- Internet (17.5%)
- CDC (17.0%)
- Friends (14.8%)
- Less commonly cited: traditional media, alternative health care provider, "other", and "none of these"

HealthStyles 2011 (preliminary data)

What Determines Credibility? Low Concern Settings

All other factors

15-20%

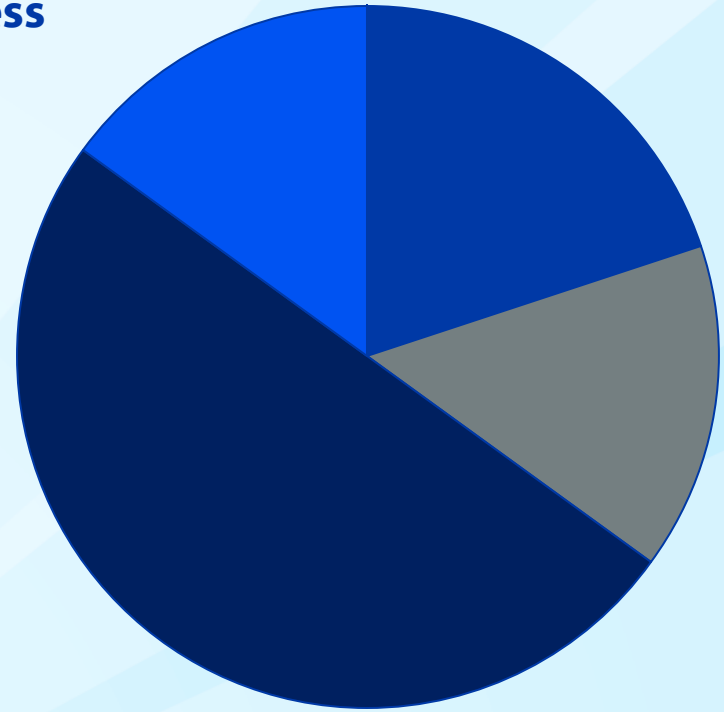


Competence/ Expertise

80-85%

Randall Hyer, NIC, 2005

What Determines Credibility? High Concern Settings



Randall Hyer, NIC, 2005

Provider Resources for Vaccine Conversations with Parents

- **Developed with partners: AAP and AAFP**
- **Primary target audience: healthcare professionals**
  - Provide information to help when talking to parents about vaccines, vaccine-preventable diseases, and vaccine safety
  - Dual purpose: resources healthcare providers can provide to parents
- **Based on formative, mixed methods research**
- **Using risk communication principles**
- **Extensively reviewed by subject matter experts**

Talking with Parents about Vaccines for Infants

- **Healthcare providers are parents' most trusted source of information about vaccines**
- **Communication strategies**
  - Take time to listen and solicit questions
  - Acknowledge parents' feelings and emotions, including their desire to protect their children
  - Remind parents that you know their infant's health is their top priority, and it's yours too
  - Don't cut off the conversation
  - Be prepared to use both science and your personal experience
  - Acknowledge risks and benefits
  - Respect parents' authority
- **Reduce the stress of shots**
- **Document parents' questions and concerns**

http://www.cdc.gov/vaccines/spec-grps/hcp/downloads/talk-infants-color-office.pdf

It's Everyone's Job

Nurses, physician assistants, and other office staff play a key role in establishing and maintaining a practice-wide commitment to communicating effectively about vaccines and maintaining high vaccination rates.

From providing parents with educational materials, to being available to answer their questions, to making sure that families who may opt for extra visits for vaccines make and keep vaccine appointments, it's everyone's job.

http://www.cdc.gov/vaccines/spec-grps/hcp/downloads/talk-infants-color-office.pdf

www.cdc.gov/vaccines

www.cdc.gov/vaccines/conversations

www.cdc.gov/vaccinesafety

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov