

Vaccine Safety Processes: Pre-Post Licensure Trials & Monitoring

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- ◆ **Disclosure**

- clinical research grants: Novartis
- speakers bureau: sanofi pasteur, Merck

- ◆ **Discussion**

- vaccines not approved by FDA
- “off label” use of FDA approved vaccines

Vaccine Safety Processes: Pre-Post Licensure Trials & Monitoring

- ◆ Vaccine development
- ◆ Vaccine licensure
- ◆ Safety monitoring
- ◆ Concerns
- ◆ Hesitancy
- ◆ AB2109
- ◆ Addressing hesitancy

Vaccine Development

- ◆ Identify causative organism
- ◆ Understand biology and pathogenesis of disease agent
- ◆ Purify the organism
- ◆ Develop vaccine
- ◆ Test vaccine
- ◆ Manufacture product
- ◆ Deliver vaccine to target population

Vaccine Regulation--Premarketing Phase: Investigational New Drug (I)

- ◆ **Preclinical**
 - laboratory characterization
 - animal testing
- ◆ **Phase I**
 - initial testing in humans
 - » adult volunteers
 - small number of subjects
 - primary concern: safety

Vaccine Regulation--Premarketing Phase: Investigational New Drug (II)

◆ Phase II

- larger studies
- target population
- safety
- immunogenicity

◆ Phase III

- larger studies
- more thorough assessment of safety
- efficacy

Vaccine Regulation: License Application

- ◆ **FDA review**
 - **vaccine study data**
 - » **safety and efficacy**
 - **manufacture**
 - » **plant evaluation**
 - » **production protocols**
 - » **quality testing**

Vaccine Regulation: Postmarketing Phase

- ◆ **Studies for additional indications**
- ◆ **Continued surveillance of vaccine lots**
- ◆ **Continued inspection of production facilities**
- ◆ **Adverse reaction reports**

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2014.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE (FIGURE 2)).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13–15 yrs	16–18 yrs
Hepatitis B ¹ (HepB)	1 st dose	← 2 nd dose →			← 3 rd dose →					[Green bar]						
Rotavirus ² (RV) RV1 (2-dose series); RV5 (3-dose series)			1 st dose	2 nd dose	See footnote 2											
Diphtheria, tetanus, & acellular pertussis ³ (DTaP: <7 yrs)			1 st dose	2 nd dose	3 rd dose				← 4 th dose →			5 th dose				
Tetanus, diphtheria, & acellular pertussis ⁴ (Tdap: ≥7 yrs)														(Tdap)		
<i>Haemophilus influenzae</i> type b ⁵ (Hib)			1 st dose	2 nd dose	See footnote 5				← 3 rd or 4 th dose → See footnote 5							
Pneumococcal conjugate ⁶ (PCV13)			1 st dose	2 nd dose	3 rd dose				← 4 th dose →							
Pneumococcal polysaccharide ⁶ (PPSV23)																
Inactivated poliovirus ⁷ (IPV) (<18 yrs)			1 st dose	2 nd dose	← 3 rd dose →						4 th dose					
Influenza ⁸ (IIV; LAIV) 2 doses for some: See footnote 8					Annual vaccination (IIV only)						Annual vaccination (IIV or LAIV)					
Measles, mumps, rubella ⁹ (MMR)							← 1 st dose →					2 nd dose				
Varicella ¹⁰ (VAR)							← 1 st dose →					2 nd dose				
Hepatitis A ¹¹ (HepA)							← 2-dose series, See footnote 11 →									
Human papillomavirus ¹² (HPV2: females only; HPV4: males and females)														(3-dose series)		
Meningococcal ¹³ (Hib-Men-CY ≥ 6 weeks; MenACWY-D ≥ 9 mos; MenACWY-CRM ≥ 2 mos)			See footnote 13											1 st dose		Booster

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages during which catch-up is encouraged and for certain high-risk groups

Not routinely recommended

Vaccine-Preventable Diseases: Baseline 20th Century & Current Morbidity

Disease	Number of Cases		% Decrease
	Baseline	2013	
Smallpox	48,164	0	100.00
Diphtheria	175,885	0	100.00
Measles	503,282	187	99.96
Mumps	152,209	584	99.62
Pertussis	147,271	28,639	80.55
Polio (par.)	16,316	1	99.99
Rubella	47,745	9	99.98
CRS	823	1	99.88
Tetanus	1,314	26	98.02
Hib	20,000	26	99.87

Post-Licensure Vaccine Safety Monitoring

- ◆ **CDC/FDA**
 - Vaccine Adverse Events Reporting System (VAERS)
 - Vaccine Safety Datalink (VSD)
- ◆ **Manufacturer**
 - Post marketing studies

Vaccine Adverse Events Reporting System (VAERS)

- ◆ National post-licensure safety surveillance system jointly operated by CDC and FDA
- ◆ Spontaneous reporting system in existence since 1990
 - reports submitted by clinicians, manufacturers, patients/parents and others
- ◆ Subject to well-described limitations of passive surveillance

VAERS

◆ Advantages

- covers US population
- permits monitoring for known adverse events
- detects signals for previously unrecognized /rare adverse events
- generates hypothesis

◆ Limitations

- risk of underreporting or overreporting
- incomplete data
- lack of availability of denominator data

VAERS HPV Data: Venous Thromboembolism

- ◆ **Total reports: 65; US reports: 41**
 - Pending evaluation: 6; Unable to follow-up or “no case”: 17
 - Confirmed cases: 18
 - » **Hormonal contraception current use (n=14)**
 - 12 cases – Oral Contraceptive Pills
 - 2 cases on Nuvaring (increase risk of clots)
 - Some have additional risk factors
 - » **No hormonal contraception use (n=4)**
 - 1 case of pregnancy
 - 1 case obesity, smoking, truck driver
 - 1 case long bus ride preceded to the VTE onset
 - 1 case had no reported risk factors

Vaccine Safety Datalink (VSD)

Participating VSD HealthCare Organizations



Rapid Cycle Analysis, VSD

Outcome	Exposure window (days)	Medical Setting	Signal?
Guillain Barré Syndrome (GBS)	1 to 42	All	NO
Seizures	0 to 42	Inpatient, ED	NO
Syncope	0	All	NO
Appendicitis	0 to 42	Inpatient, ED	NO
Stroke	0 to 42	Inpatient, ED	NO
Venous Thromboembolism (VTE)	1 to 42	All	NO
Anaphylaxis	0 to 2	All	NO
Other Allergic rxns	0 to 2*	All	NO

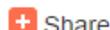


Vaccine Safety

Vaccine Safety

[Vaccines Safety Basics](#)[Addressing Common Concerns](#)[Vaccine Monitoring](#)[Activities](#)[About Immunization Safety Office \(ISO\)](#)

► Clinical Immunization Safety Assessment (CISA) Project

[CISA Clinician Resources](#)[CISA Evaluation](#)[Current Studies](#)[Historical Background 2001-2012](#)[Publications & Technical Reports](#)[Emergency Preparedness](#)[Vaccine Adverse Event Reporting System \(VAERS\)](#)[Vaccine Safety Datalink \(VSD\)](#)[Archived Activity Documents](#)[Specific Groups of People](#)[Resource Library](#)[Vaccine Safety > Activities](#)

Clinical Immunization Safety Assessment (CISA) Project

CDC's Clinical Immunization Safety Assessment (CISA) Project was established in 2001 to address the unmet vaccine safety clinical research needs of the United States.

CISA is a national network of vaccine safety experts from the CDC's Immunization Safety Office (ISO), seven medical research centers, and other partners, which provides a comprehensive vaccine safety public health service to the nation.

On this Page

- [Current CISA Project Sites](#)
- [CISA Mission](#)
- [CISA Goals](#)
- [CISA Current Activities](#)

To request a CISA Clinical Consultation:

If you are a US healthcare provider with a vaccine safety question about a specific patient residing in the US, you can contact CISA at CISAeval@cdc.gov to request a case evaluation. This service is provided free of charge. View [here](#) for more information.



Current CISA Project Sites

- [Boston Medical Center](#)
- [Cincinnati Children's Hospital Medical Center](#)
- [Columbia University](#)
- [Duke University](#)
- [Johns Hopkins University](#)
- [Kaiser Permanente Northern California](#)
- [Vanderbilt University](#)

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Contact Us:

Centers for Disease Control and Prevention
1600 Clifton Rd
Atlanta, GA 30333

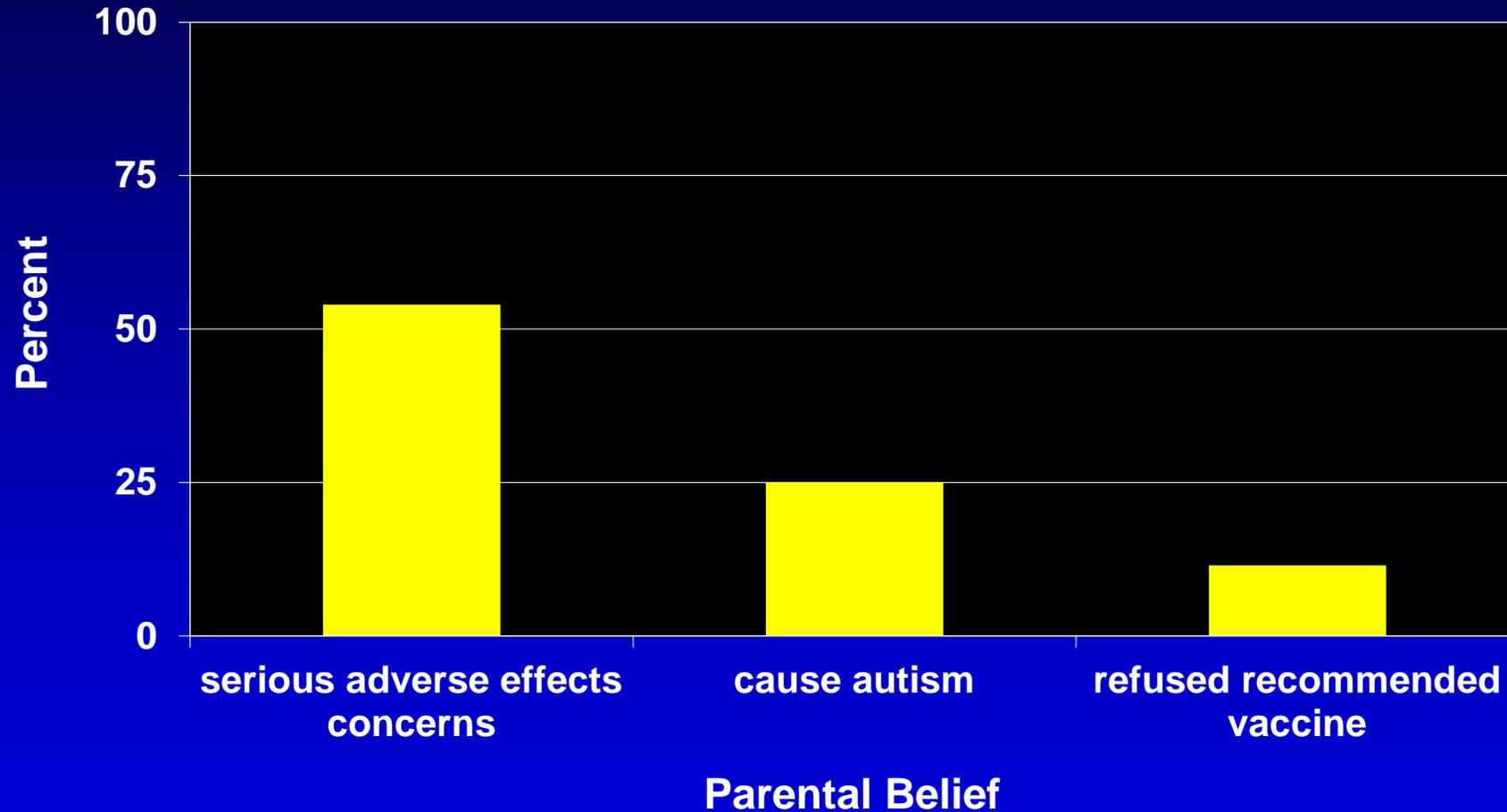
800-CDC-INFO
(800-232-4636)
TTY: (888) 232-6348

[Contact CDC-INFO](#)

Vaccine Adverse Event Myths

- ◆ **No credible scientific evidence that vaccines cause:**
 - autism
 - multiple sclerosis
 - diabetes
 - asthma
 - inflammatory bowel disease
 - SIDS
 - overwhelm immune system

Parental Vaccine Safety Concerns



Overwhelm Immune System?

- ◆ **Infant immune system**
 - naïve
 - can respond to thousands of antigens simultaneously
- ◆ **Challenges other than vaccines**
 - natural environmental exposures
 - » strep throat: >50 antigens
 - » otitis media: >2,000 antigens

Number of Immunogens in Vaccines

1900		1960		1980		2014	
Vaccine	Immunogens	Vaccine	Immunogens	Vaccine	Immunogens	Vaccine	Immunogens
Smallpox	~200	Smallpox	~200	Diphtheria	1	Diphtheria	1
		Diphtheria	1	Tetanus	1	Tetanus	1
		Tetanus	1	Pert-WC	~3000	Pert-AC	2-5
		Pert-WC	~3000	Polio	15	Polio	15
		Polio	15	Measles	10	Measles	10
				Mumps	9	Mumps	9
				Rubella	5	Rubella	5
						Hib	2
						Varicella	69
						PCV	14
						Hepatitis B	1
						Hepatitis A	1
						MCV	4
						RV	2-7
						HPV	4
						Influenza*	6-114
Total	~200	Total	~3217	Total	~3041	Total	142-258

Thimerosal Concerns: Neurotoxin?

- ◆ **Thimerosal**
 - preservative
 - ethylmercury
- ◆ **Toxicity data**
 - methylmercury
- ◆ **7 well done studies**
 - methods
 - » both retrospective & prospective
 - » ecological & cohort
 - » several 100,000 children
 - results: no association

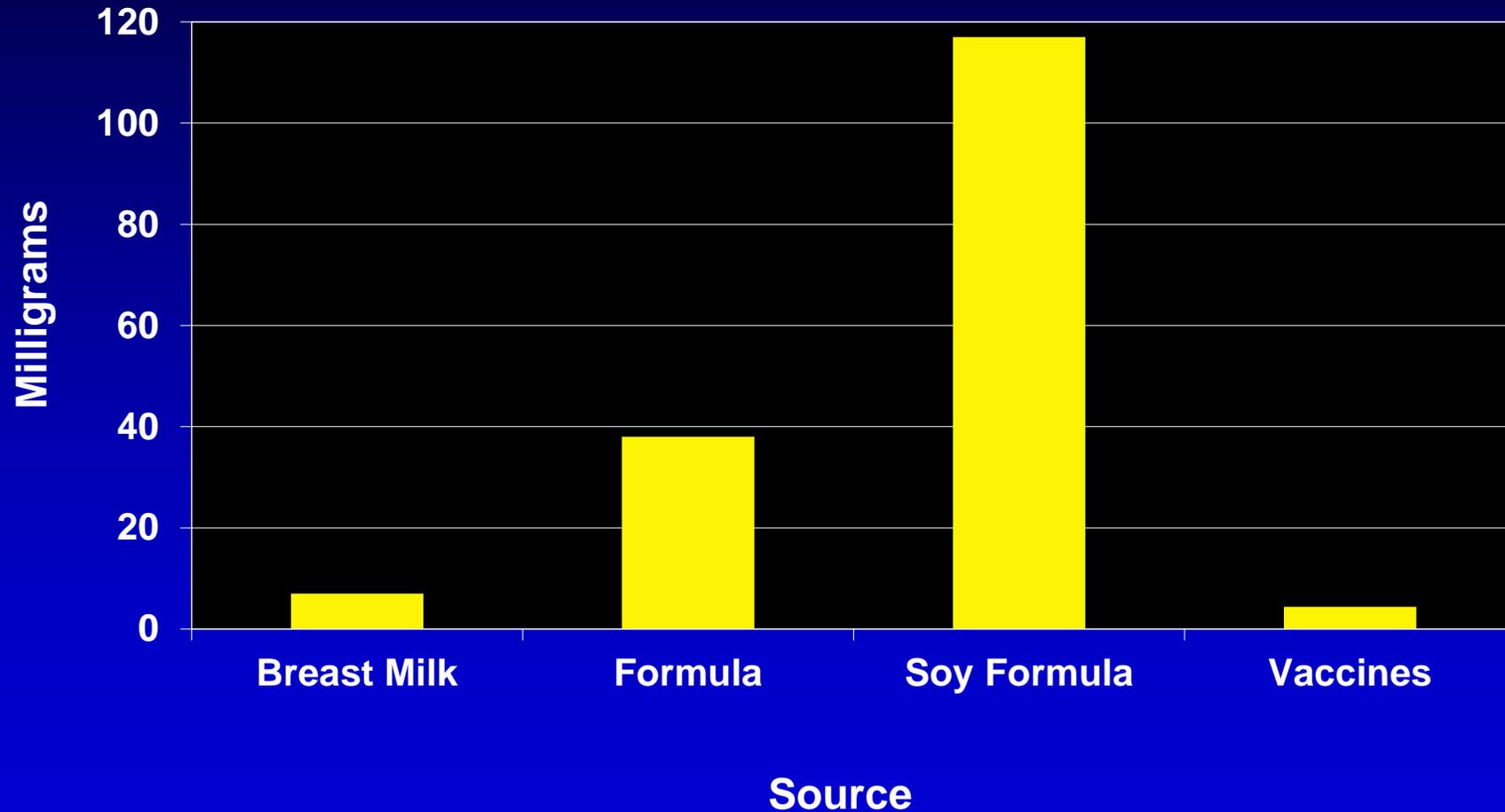
Thimerosal Content: US Vaccines

Vaccine	Trade name	Manufacturer	Thimerosal Concentration
DTaP	Tripedia [®]	Sanofi Pasteur	≤0.00012%
	Infanrix [®]	GlaxoSmithKline	0
	Daptacel [®]	Sanofi Pasteur	0
DTaP-HepB-IPV	Pediarix [®]	GlaxoSmithKline	0
Tdap	Adacel [®]	Sanofi Pasteur	0
	Boostrix [®]	GlaxoSmithKline	0
<i>Haemophilus influenzae</i> type b conjugate (Hib)	ActHIB [®]	Sanofi Pasteur	0
	PedvaxHIB [®]	Merck & Co, Inc	0
Hib/Hepatitis B combo	Comvax [®]	Merck & Co, Inc	0
Hepatitis B	Engerix B [®]	GlaxoSmithKline	0
	Recombivax HB [®]	Merck & Co, Inc	0
Hepatitis A/Hepatitis B	Twinrix [®]	GlaxoSmithKline	<0.0002%
Influenza*	Various	Various	Varies

Aluminum Concerns

- ◆ **Aluminum in vaccines**
 - adjuvant
 - maximum amount 0.85 mg/dose
- ◆ **Aluminum exposure**
 - deodorant
 - food
 - » adults average 7-9 mg/day
 - 200 mg in antacids
 - breast milk
 - » 0.04 mg/L
 - formula
 - » 0.225 mg/L

Aluminum Exposure: 1st 6 Months of Life

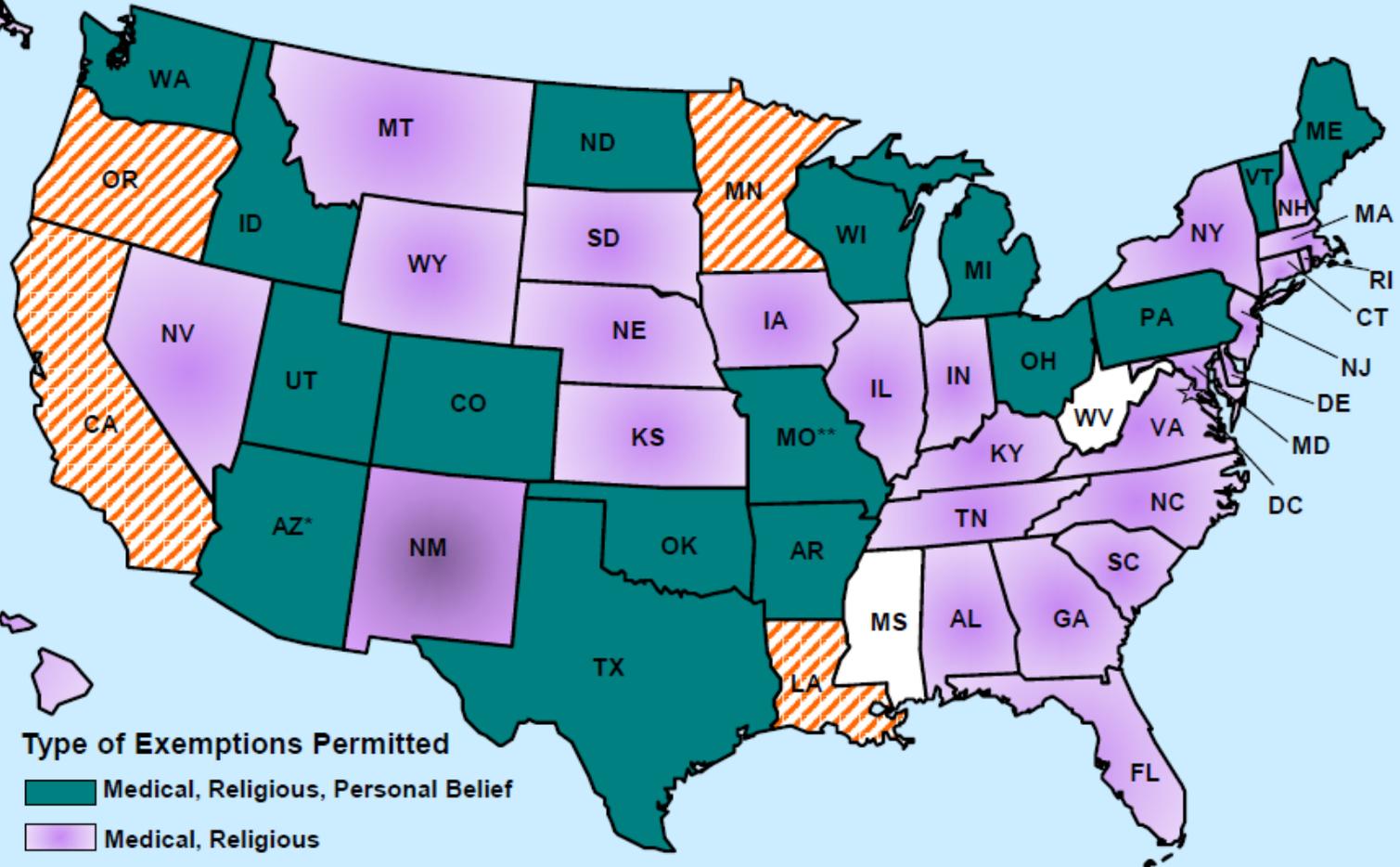


MMR & Autism

- ◆ **1998: Wakefield Lancet publication**
 - case series
 - » 12 children
- ◆ **Biological plausibility: no**
- ◆ **10 well done studies**
 - methods
 - » both retrospective & prospective
 - » ecological & case control
 - » millions of children
 - results: no association

Exemptions Permitted to School and Childcare Immunization Requirements

June 2014



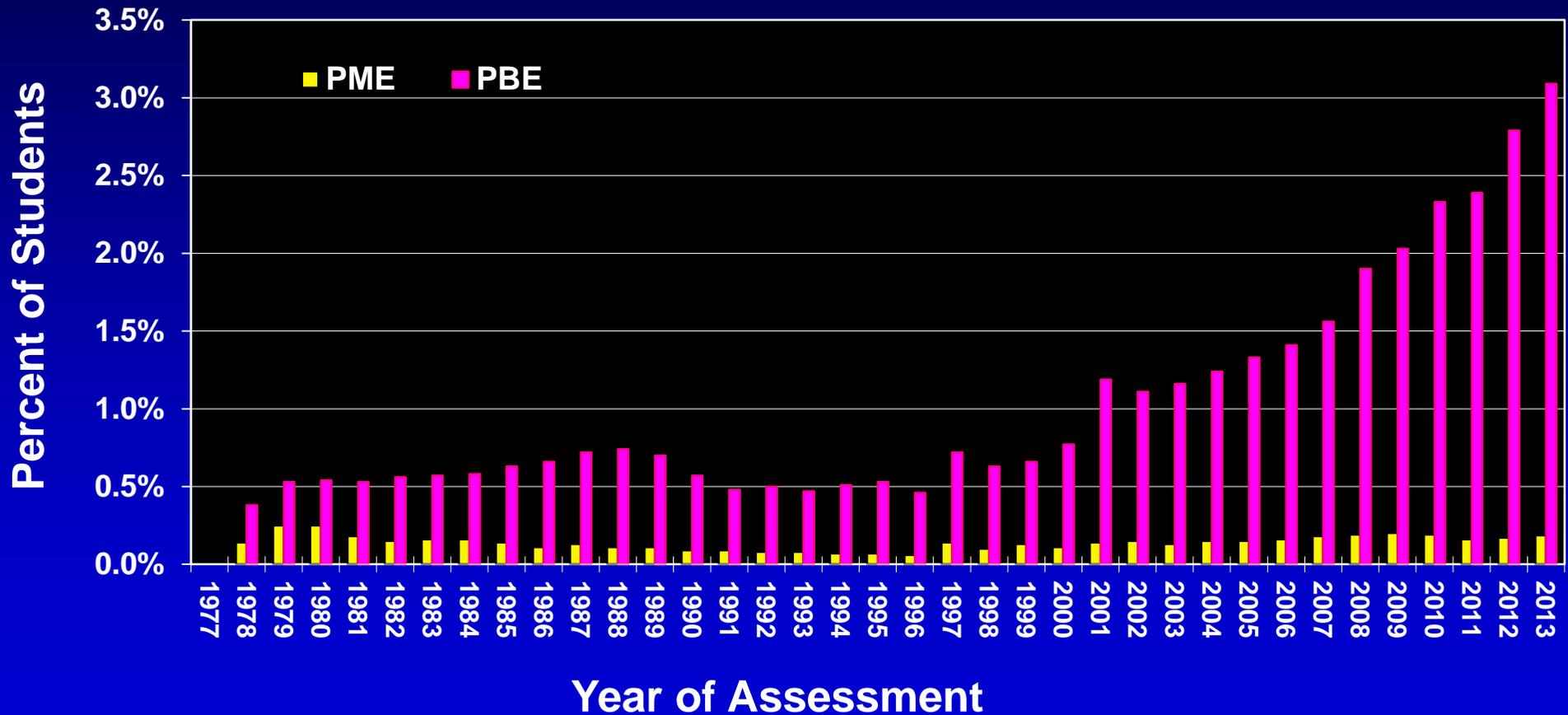
Type of Exemptions Permitted

- Medical, Religious, Personal Belief
- Medical, Religious
- Medical, Personal Belief
- Medical Only

* Arizona: Personal belief exemption permitted for school only

**Missouri: Personal belief exemption permitted for childcare only

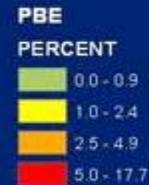
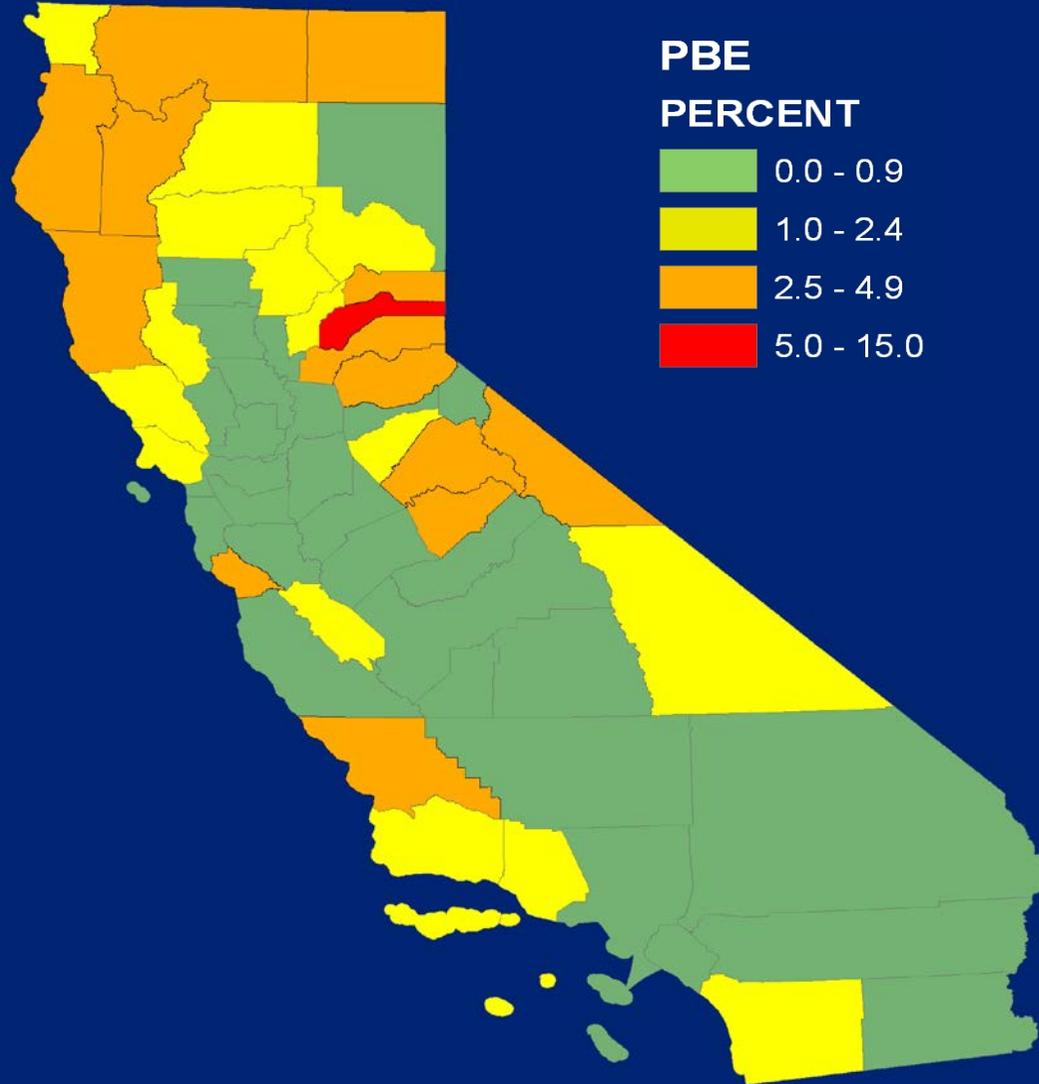
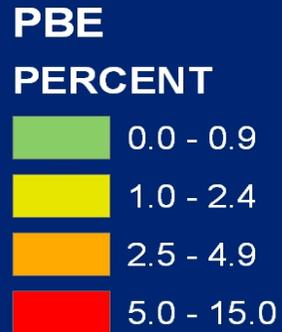
Permanent Medical Exemptions & Personal Beliefs Exemptions, Kindergarten Students, California



Kindergarten PBEs by County

2000

2010



AB2109: Implementation

- ◆ **Effective January 1, 2014**
- ◆ **Parents wanting to exempt their children from one or more required immunizations**
 - must use form
- ◆ **Students affected**
 - newly admitted to CA school (K-12th)
 - advancing to 7th grade
 - newly admitted to child care
- ◆ **Form must be signed no sooner than 6 months before admission to school/child care/advancing to 7th grade**

AB2109: Health Care Providers

- ◆ **Provide information**
 - benefits and risks of required immunizations
 - health risks of specific vaccine-preventable diseases to child and community
- ◆ **Sign form along with parent**
 - only parent signs for religious exemption
- ◆ **Who can sign form**
 - MD, DO, NP, PA, naturopathic doctor, credentialed school nurse

Vaccine Hesitant Parents

◆ Concerns

- vaccines highly purified
 - » immune system not overwhelmed
 - » no thimerosal in virtually all routine pediatric vaccines
 - » aluminum vaccine content trivial vs. environment
- no MMR association with autism

◆ Vaccine schedule

- protect children when they are most vulnerable
- delayed vaccines = delayed protection

Parental Immunization Refusal

- ◆ **Listen carefully to concerns**
 - encourage questions
- ◆ **Discuss known risks and benefits**
 - risks to unimmunized child
- ◆ **Concerns about specific vaccines**
 - discuss
 - administer other vaccines
- ◆ **Multiple injection concerns**
 - modify schedule
- ◆ **Revisit discussion in future visits**
- ◆ **Document**

Vaccine Safety Discussion Strategies

- ◆ **Empathize: acknowledge that there are many conflicting messages in the media**
- ◆ **Assess level of scientific evidence desired**
- ◆ **Maximize benefits to their child**
 - not a public health discussion
 - vaccines provide protection
 - risk of disease for omitted vaccines
- ◆ **Provide appropriate resources**
 - e.g., CDC, AAP, NNII, CHOP

Continued Vaccine Refusal

◆ Challenges

- time commitment for discussions
 - » frustration

◆ Agree to disagree

- acknowledge differences
 - » “it sounds like you and I have different philosophies”
- offer referral to a different practice/clinic
 - » “you might be more comfortable with this group”

Vaccine Safety Processes: Pre-Post Licensure Trials & Monitoring--Summary

- ◆ Many vaccine-preventable disease successes
- ◆ Safety concerns
 - hesitancy
- ◆ New PBE process
- ◆ Addressing hesitancy