

How do you measure efficacy and safety?

Philip LaRussa, M.D.

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Vaccine Efficacy vs. Effectiveness

CDC definition

- Vaccine efficacy and vaccine effectiveness measure the proportionate reduction in cases among vaccinated persons.
 - **Efficacy** is used when a study is carried out under ideal conditions, for example, during a clinical trial.
 - **Effectiveness** is used when a study is carried out under typical field (that is, less than perfectly controlled) conditions.
- **Vaccine efficacy and effectiveness (VE)** are measured by calculating the risk of disease among vaccinated and unvaccinated persons and determining the percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons.
 - The greater the percentage reduction of illness in the vaccinated group, the greater the vaccine efficacy/effectiveness.

= (Risk among unvaccinated group – risk among vaccinated group)

Risk among unvaccinated group

Distinguishing vaccine efficacy and effectiveness

- **Vaccine efficacy:**

- The protective effects of vaccination by the reduction in the infection risk of a vaccinated **individual** relative to that of a susceptible, unvaccinated individual

- **Vaccine effectiveness:**

- **Population-level** vaccine effectiveness categorized into the 'direct', 'indirect', 'total' and 'overall' impact of the vaccine

- **Direct effects** compares the direct risk of a randomly selected individual **with and without the vaccination program**
- **Indirect effects** can be estimated from the difference in the degree of protection that unvaccinated individuals receive in the **presence vs. the absence of a vaccine program**.
- **'Total' effectiveness** measures the relative infection risk in vaccinated individuals compared to the infection risk in unvaccinated individuals **before a vaccination program is launched**
 - Thus, 'total' effectiveness of vaccination is the effect of the vaccination program combined with the effect of the person having been vaccinated
 - **Does not take into account indirect protection of unvaccinated individuals in a partially vaccinated population.**
- **'Overall' effectiveness** of a vaccination program is defined as the reduction in the transmission rate for an **average individual in a population with a vaccination program** at a given level of coverage compared to an **average individual in a comparable population with no vaccination program**
 - **'Overall' effectiveness takes into account benefits to both vaccinated and unvaccinated individuals**

Drug Approval Process

- FDA's Center for Biologics Evaluation and Research (CBER)
- FDA Investigational New Drug (IND) Application
 - **Pre-IND Consultation Program**
 - Sponsor submits:
 - **Animal Pharmacology & Toxicology Studies:** permits an assessment as to whether the product is reasonably safe for initial testing in humans
 - **Manufacturing Information:** composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product.
 - **Clinical Protocols and Investigator Information:** detailed protocols for proposed clinical studies to assess whether the trials will expose subjects to unnecessary risks
 - **30-day FDA review period**
 - Clinical hold or go ahead
 - **Assembly of an independent Data Safety Monitoring Committee**
- Phase I, II, III Clinical Trials

Drug Approval Process

- **Clinical Trials data submitted to the FDA**
 - FDA request for additional data?
 - If successful, then:
 - **Biologics License Application (BLA):**
 - Multidisciplinary FDA review team (medical officers, microbiologists, chemists, biostatisticians, etc.) reviews efficacy & safety information, makes a risk/benefit assessment
 - Recommends, or opposes the approval of a vaccine
 - **Pre-approval inspection of proposed manufacturing facility** where the vaccine is in production

FDA Drug Approval Process

- **Presentation to the Vaccine Related Biologic Product Advisory Committee (VRBPAC)**
 - External review panel recommendation
 - **FDA approval for specific indications warranted by the clinical trials data presented to the FDA**
- **Product insert content & Recommendations for Phase IV studies:**
 - <https://www.fda.gov/media/94583/download>
- **Post-licensure FDA functions**
 - Monitor the product & production activities
 - Periodic facility inspections
 - May require submission of results of tests for potency, safety, and purity for each vaccine lot
 - May require submission of samples of each vaccine lot to the FDA for testing

Post-Approval Period

- **Review by Other Independent Advisory Committees**
 - Harmonized recommendations from the CDC Advisory Committee on Immunization Practices (**ACIP**), **American Academy of Pediatrics**, Academy of Family Practice
 - Usually consistent with FDA-approved indications
 - Recommend/ not recommend use of the vaccine
 - Universal vs. targeted immunization strategy?

Emergency Use Authorization (EUA)

- Under section 564 of the Federal Food, Drug, and Cosmetic Act ([FD&C Act](#)), the FDA Commissioner may **allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency** to diagnose, treat, or prevent serious or life-threatening diseases or conditions **caused by CBRN (Chemical, Biological, Radiological, and Nuclear) threat agents when there are no adequate, approved, and available alternatives.**
- Section 564 of the FD&C Act was amended by the [Project Bioshield Act of 2004](#) and was further amended by the [Pandemic and All-Hazards Preparedness Reauthorization Act of 2013](#) (PAHPRA), the [21st Century Cures Act](#) of 2016, and [Public Law 115-92](#) of 2017.
- **A determination under section 319 of the Public Health Service Act that a public health emergency exists**, such as the [one issued on January 31, 2020](#), **does not enable FDA to issue EUAs.**
- **A separate determination and declaration are needed** under section 564 of the Federal Food, Drug and Cosmetic Act to enable FDA to issue EUAs, provided other statutory criteria are met.

How do you measure vaccine efficacy?

- Pre-licensure Phase I, II, III studies
- Disease prevention:
 - pathogen specific clinical presentation vs. ILI or pneumonia
- Surrogate markers:
 - Validated immunogenic markers that correlate with clinical efficacy
 - Scar/ smallpox vaccine site
 - Validated antibody titers: ≥ 1 mcg/ml anticapsular H. influenzae type b antibody at 1 year post immunization
- Post-licensure (Phase IV) study design: cohort, case control, ecological, risk interval analyses?

Initial Safety & Efficacy Studies

- **In vitro studies:**
 - Cellular metabolism
 - Cell-specific toxicity
 - Oncogenic potential in mammalian cells
- **Animal studies if an appropriate animal model is available:**
 - Pathogenicity of virus or bacteria
 - Transmissibility
 - Development of immunity
 - Initial testing of potential vaccine candidates
 - Preliminary assessments of vaccine safety

Vaccine Clinical Trials

- **Phase I Clinical Trials**

- 1st testing of vaccine in humans
- Small (20-80 participants)
- Start with adults
- Can include placebo
- Often open-label
- **Endpoints are safety and immunogenicity**
 - Monitor for adverse events and antibody response
 - Test dosing

Vaccine Clinical Trials

- **Phase II clinical trials**
- Blinded, placebo controlled
 - **Phase IIa**
 - Larger version of Phase I (several hundred subjects)
 - Product defined – including manufacturing steps:
 - i.e. testing of various formulations
 - **Phase IIb**
 - Larger than Phase IIa
 - Continue to test safety and immunogenicity
 - Can sometimes establish efficacy

Phase III Clinical Trials

- “Pivotal studies” - randomized, double-blind, **placebo-controlled**
- Thousands of subjects
- Diverse populations
- **Demonstrate vaccine efficacy:**
 - Reduction in a **defined clinical disease** (i.e. I.L.I., chickenpox rash)
 - Reduction in **disease intermediary** (i.e. cervical intraepithelial neoplasia after HPV infection)
 - Determine **correlation between immune response (i.e. antibody levels) and disease protection**
- **Better define vaccine safety**
 - May require very large numbers of participants
 - Active monitoring for adverse events
 - Able to detect common side effects
 - Safety of adjuvant

Alternatives to Randomized Placebo-Controlled Clinical Trial Designs?

- Placebo use is not thought to be ethical due to high mortality risk
- The vaccine candidate is likely to be safe and effective
- It would be difficult to get vaccine to all segments of a population at the same time due to logistical or financial reasons

Alternatives to Randomized Placebo-Controlled Clinical Trial Designs?

- **Just vaccinate the entire population at the same time (ecological study)**
- **Ring Vaccination Cluster-randomized Trial:**
 - 2015 Phase III trial in Guinea of a Zaire strain Ebolavirus vaccine
 - Trial population: **clusters of all contacts and contacts of contacts of laboratory-confirmed Ebola cases, randomly assigned to immediate, or delayed vaccination**
 - Required a robust contact tracing system
 - <https://www.thelancet.com/action/showPdf?pii=S0140-6736%2815%2961117-5>
- **Ordered Stepped-Wedge Cluster Trial Design:**
 - Trial population: **geographically distinct clusters that are randomly, and sequentially assigned to vaccination**
 - 2014, Liberia Ebola vaccine trial
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4979980/pdf/pntd.0004866.pdf>

Post-licensure (Phase IV) studies

- **Required as a condition of FDA approval**
 - Industry sponsored
 - $\geq 10,000$ participants
 - Better than Phase III but still limited
- **Observational, use large administrative databases**
 - Identify rare reactions
 - Monitor increases in known reactions
 - Identify risk factors for reactions
 - Identify vaccine lots with unusual rates or types of events
 - Identify signals for new events
 - Assess safety in special populations
 - Role of registries, etc.

How do you measure vaccine effectiveness?

- **Post-licensure study designs:**

- **Case-control Study:**

- Varicella vaccine effectiveness

- Potential cases of chickenpox identified by active surveillance of pediatric practices in New Haven, Connecticut, area(3/97-11/00)
- **Cases:** children with PCR-confirmed varicella
- **2 controls per case**, matched by both age and pediatric practice.
- 23% of 202 children with PCR-confirmed varicella and 61% of 389 matched controls had received the vaccine (vaccine effectiveness, 85% (95% C.I. 78-90%; $P < 0.001$))
- Against moderately severe and severe disease the vaccine was 97% effective (95% C.I. 93-99%)

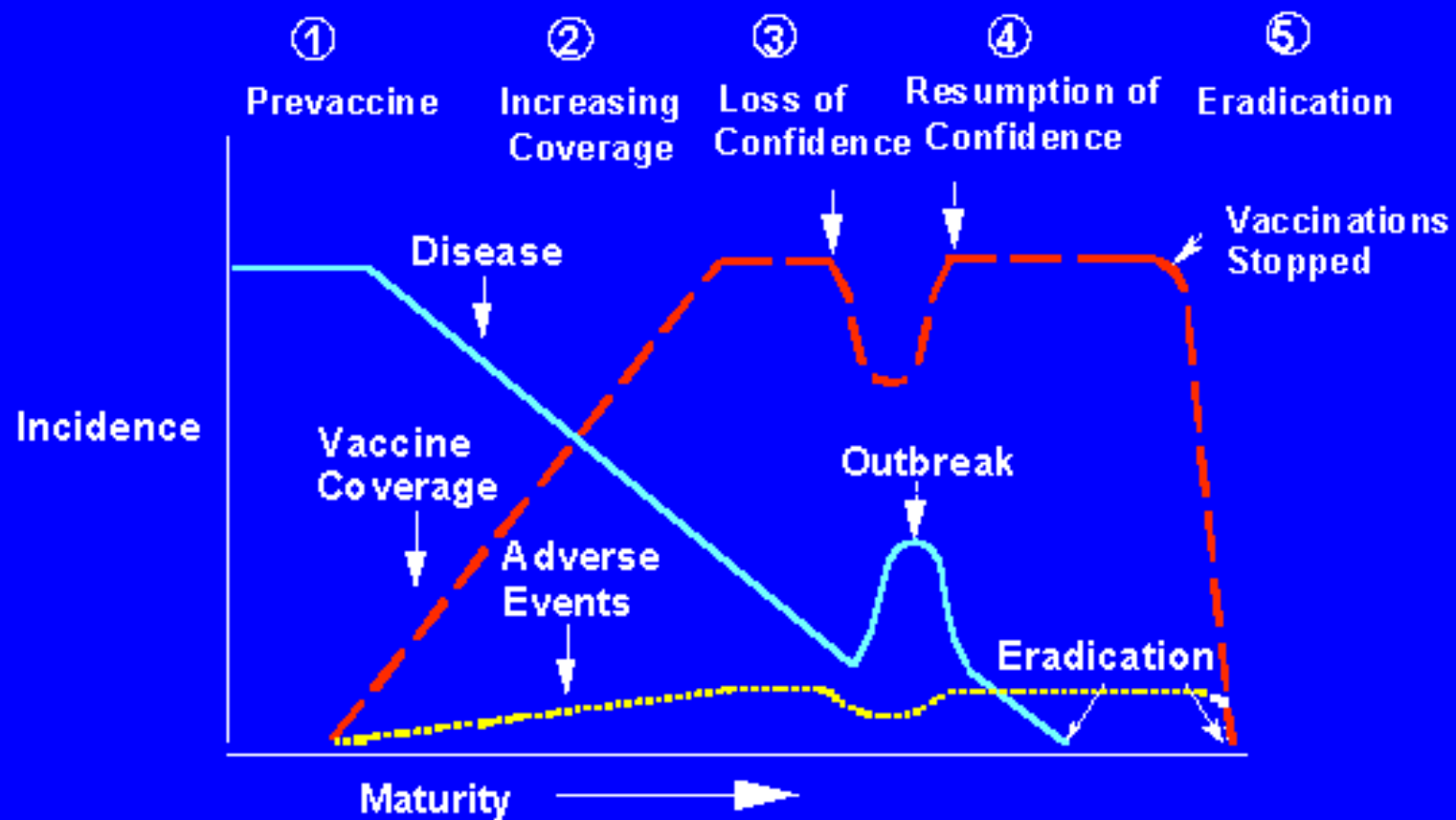
How do you measure vaccine effectiveness?

- Post-licensure study design:
 - **Cohort studies:**
 - Longitudinal data on individual subjects is available
 - Can be retrospective or prospective
 - Ex: active surveillance for disease in group of children born in a particular year
 - Can compare years prior to and after introduction of vaccine or different areas where vaccine is or is not available over the same time period
 - Subject to time-related bias
 - **Ecological studies:**
 - Aggregate population data, no individual data
 - Ex: using aggregate data on disease prevalence before and after introduction of vaccine to assess efficacy
 - Fallacy of association

Importance of Vaccine Safety

- Decrease in disease risks → increased attention on risks attributed to vaccines
- **Public confidence in vaccine safety is critical for maintaining high vaccine coverage rates**
 - **Higher standard of safety expected of vaccines**
 - Vaccinees are generally healthy
 - Lower risk tolerance for vaccines in absence of widespread vaccine-preventable diseases:
 - Need to search for rare reactions
 - Vaccination is universally recommended and mandated in many states

Evolution of Immunization Program and Prominence of Vaccine Safety



Immunization Safety Issues

- Anticipating safety issues, e.g., antibody enhanced disease
- Preliminary safety testing
- Age dependent immune responses
- Testing in susceptible individuals vs. those with prior immunity
- Testing in special populations, e.g., immunodeficient subjects, pregnant women, children, elderly
- How safe is safe enough?
- Public perception vs. scientifically collected data
- Role of the popular media
- Vaccine hesitancy, and refusal

Anticipating safety issues: Enhanced disease after vaccination

- **Atypical measles after immunization with inactivated measles vaccine:** this is probably more an expression of a non-protective response to measles antigens and a type 2 skewing of the cytokine response after infection.
- **Inactivated RSV vaccine** may have caused severe disease after exposure to RSV by a similar mechanism as is postulated with atypical measles.
 - During early trials with inactivated RSV vaccine, the vaccine did not prevent infection, 80% of those infected required hospitalization and two children died.
 - Lung pathology in patients showed an unexpected inflammatory response with both neutrophils and eosinophils, evidence of immune complex formation and complement activation in small airways.
 - The vaccine caused a similar disease enhancement in animals characterized by immunopathology and a Th2 biased response and antibody responses with poor neutralizing activity.
- **Antibody disease enhancement (ADE) of Dengue virus infection** in humans is directly caused by non-neutralizing or sub-neutralizing antibodies leading to more efficient viral uptake via Fcγ receptor binding.

Anticipating safety issues: Enhanced disease after vaccination

- Pathology consistent with RSV vaccine enhanced disease (and perhaps ADE) has been demonstrated for some SARS CoV-1 vaccine candidates in animal models

Table 1

Evidence of enhanced disease in SARS-CoV-1 vaccine candidates.

Animal Model	Vaccine	Adjuvant	Immunopathology	Reference
Murine ¹	VEE Replicon Particles expressing N protein	–	YES	Deming 2006
Murine ²	Recombinant Vaccinia virus expressing N protein	–	YES	Yasui 2008
Murine ³	Inactivated Whole Virus	Alum	YES	Bolles 2011
		–	YES	
Murine ⁴	Replicon Particles expressing S protein	–	YES	Sheahan 2011
Murine ⁵	Inactivated Whole Virus and S protein vaccines	Alum	YES	Tseng 2012
		–	YES	
Ferret ⁶	Recombinant Modified Vaccinia Virus Ankara (rMVA) expressing S protein	–	YES [†]	Weingartl 2004
NHP ⁷	Modified Vaccinia Ankara (MVA) virus encoding full-length S protein	–	YES	Liu 2019
	Passive anti-S sera	N/A	YES	
NHP ⁷	Inactivated Whole Virus	–	YES	Wang 2016/2020
	Passive Human SARS Antiserum	N/A	YES	

¹ Young and senescent female BALB/c mice.

² BALB/c mice.

³ Aged BALB/c mice.

⁴ Young and aged BALB/c mice.

⁵ Female BALB/c mice.

⁶ *Mustela putorius furo*, castrated males.

⁷ Chinese rhesus macaque.

[†] Acute hepatitis.

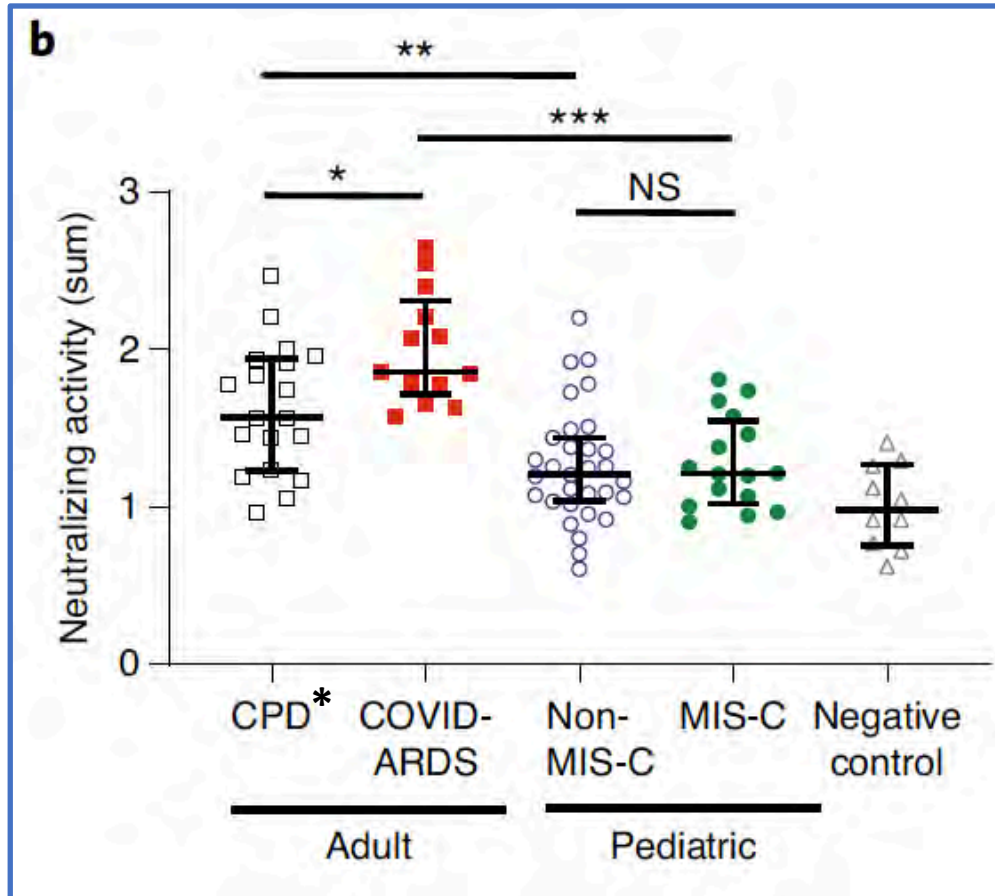
Anticipating safety issues: Enhanced disease after vaccination

- Emerging themes in the animal models:
 - High titers of neutralizing vs. non-neutralizing antibodies and a Th1 vs. a Th2 mediated inflammatory response decrease the likelihood of enhanced disease
 - Class I fusion proteins (such as S protein) are common among enveloped viruses including RSV, parainfluenza viruses, and coronaviruses and have been successfully stabilized in their prefusion conformations by insertion of 2 proline residues.
 - preserves neutralization-sensitive epitopes, avoid antibodies that are non-neutralizing, and improve expression in transfected cells

Age dependent immune responses

- In children < 2 years of age:
 - T cell independent response to capsular polysaccharide antigens
 - T-cell dependent response when the same polysaccharide is conjugated to a protein molecule

Differences in immune responses to COVID infections in adults and children



*convalescent plasma donors

- **Adults** had higher neutralizing antibody titers, ADCP*, and more vigorous T cell responses to viral spike proteins compared to pediatric patients
- **Pediatric patients** had higher serum concentrations of IL-17A and IFN γ
- **Pediatric patients** who recovered without sequelae, exhibited the lowest ADCP activity and had the lowest serum concentrations of IL-6 and TNF, cytokines associated with ARDS and poor outcome in clinical studies

*antibody-dependent cellular cytotoxicity phagocytosis

Sci Transl Med. 2020 October 07; 12(564):

Testing in susceptible individuals vs. those with prior immunity:

- Uncircumcised men with high titers of antibodies to adenovirus 5 at the time of immunization with an ad5 vectored HIV vaccine were more likely to be infected with HIV compared to those vaccinees who were antibody negative to ad5 at the time of vaccination.
 - proposed mechanism is that the Ad5 vector stimulated the production of Ad-specific CD4 T cells, which were drawn to mucosal sites by natural adenovirus infection, and thus were available for infection when HIV contacted those surfaces.
- Antibody dependent enhancement in dengue in those with prior evidence of dengue infection with a different serotype

Testing in susceptible individuals vs. those with prior immunity:

- Primary Efficacy Endpoint Analysis of Moderna Study 301 (Starting 14 Days After Second Injection; Per-Protocol Set)
 - Overall, 11 (< 0.1) cases in the mRNA group (14,134) vs. 185 (1.3) cases in the placebo group (14,073); **VE= 94.1%** (89.3%, 96.8%), $p < 0.0001$. (Moderna mRNA VRBPAC briefing document)
 - **Among participants who were positive for SARS-CoV-2**, by serologic or virologic testing, at baseline (337 in the placebo group and 343 in the mRNA-1273 group), 1 case of COVID-19 was diagnosed by RT-PCR testing in a placebo recipient and no cases were diagnosed in mRNA-1273 recipients.
 - **Solicited adverse events** were less common in participants who were positive CoV-2 infection at baseline than in those who were negative at baseline

Testing in special populations

- Immunodeficient subjects:
 - Safety issues:
 - Replication competent vectors, live virus vaccines
 - Efficacy/Immunogenicity issues: can they make an adequate response?
- Children:
 - Primary aims: prevent shedding, rare severe disease?
 - Safety issues if the TH2 response predominates
 - Efficacy issues if vaccine provokes non-neutralizing antibodies
- Pregnant women: safety of the fetus vs. protection of the mother
- The elderly:
 - High titer influenza vaccine in those ≥ 65 years of age
 - Improved response of shingles vaccine with the addition of a potent adjuvant
 - Age stratification in Pfizer and Moderna mRNA vaccine studies to allow statistical power to show efficacy and safety in the elderly

Federal Government's Role in Vaccine Safety

- **National Childhood Vaccine Injury Act of 1986:**
 - Created the National Vaccine Program (NVP), and Office (NVPO), & National Vaccine Advisory Committee (NVAC)
 - Report to the Ass't Secretary of Health & Human Services
 - Coordinate and provide direction for:
 - Vaccine research & development
 - Safety and efficacy testing of vaccines
 - Licensing of vaccine manufacturers and vaccines
 - Production, procurement, distribution & use of vaccines
 - Evaluate need for & effectiveness, adverse effects of vaccines
 - Coordinate governmental and non-governmental activities

NVAC Responsibilities

- **Independent advisory committee**
- **Provide recommendations to the Director of NVP & the Assistant Secretary of Health & Human Services:**
 - Study & recommend ways to encourage the availability of an adequate supply of safe and effective vaccines
 - Recommend research priorities & other measures the Director of the Program should take to enhance the safety and efficacy of vaccines
 - Advise the Director in the implementation of sections 2102 & 2103 of Title XXI of the Public Health Service Act
 - Identify the most important areas of government and non-government cooperation that should be considered in implementing sections 2102 & 2103 of Title XXI of the Public Health Service Act

Post-licensure Vaccine Safety Activities

- **Phase IV Trials**
- **Vaccine Adverse Events Reporting System (VAERS)**
- **Vaccine Safety Datalink (VSD)**
 - Large Vaccine-Linked Databases
- **Clinical Immunization Safety Assessment (CISA)**

Vaccine Adverse Event Reporting System (VAERS)

- **National Reporting System**

- Jointly administered by CDC & FDA
- ~15,000 reports per year

- **Advantages:**

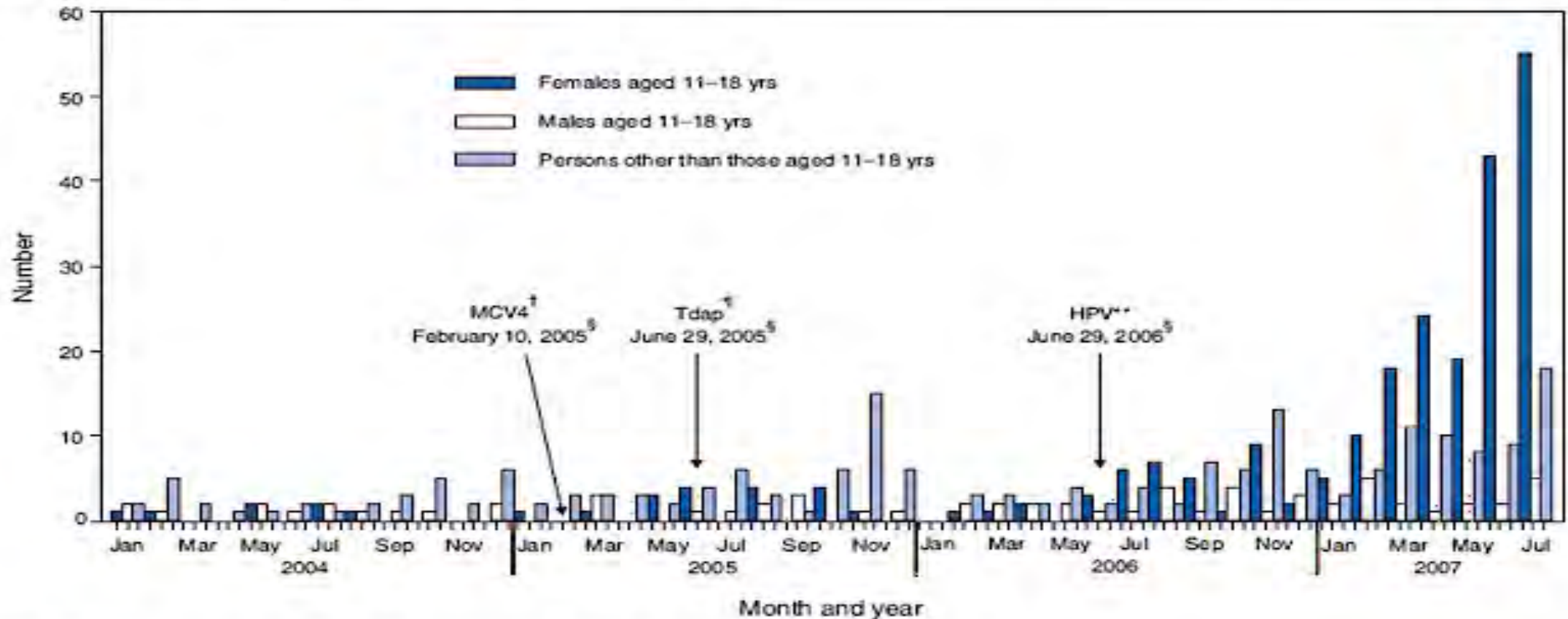
- Open to anyone to report an event
- Detects potential signals for new events

- **Limitations:**

- **No** assessment of causality:
 - Whatever is reported is recorded
- Passive & retrospective:
 - **Can't accurately assess rates** & it's difficult to get appropriate specimens

VAERS Reports of Syncope Following Vaccination

FIGURE. Number of postvaccination syncope* episodes reported to the Vaccine Adverse Event Reporting System, by month and year of report — United States, January 1, 2004–July 31, 2007



* Includes persons aged ≥ 5 years who had syncope onset after vaccination on the same date.

† Meningococcal conjugate vaccine.

‡ Date on which the Advisory Committee on Immunization Practices decided to add this newly licensed adolescent vaccine to the Vaccines for Children Program.

§ Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

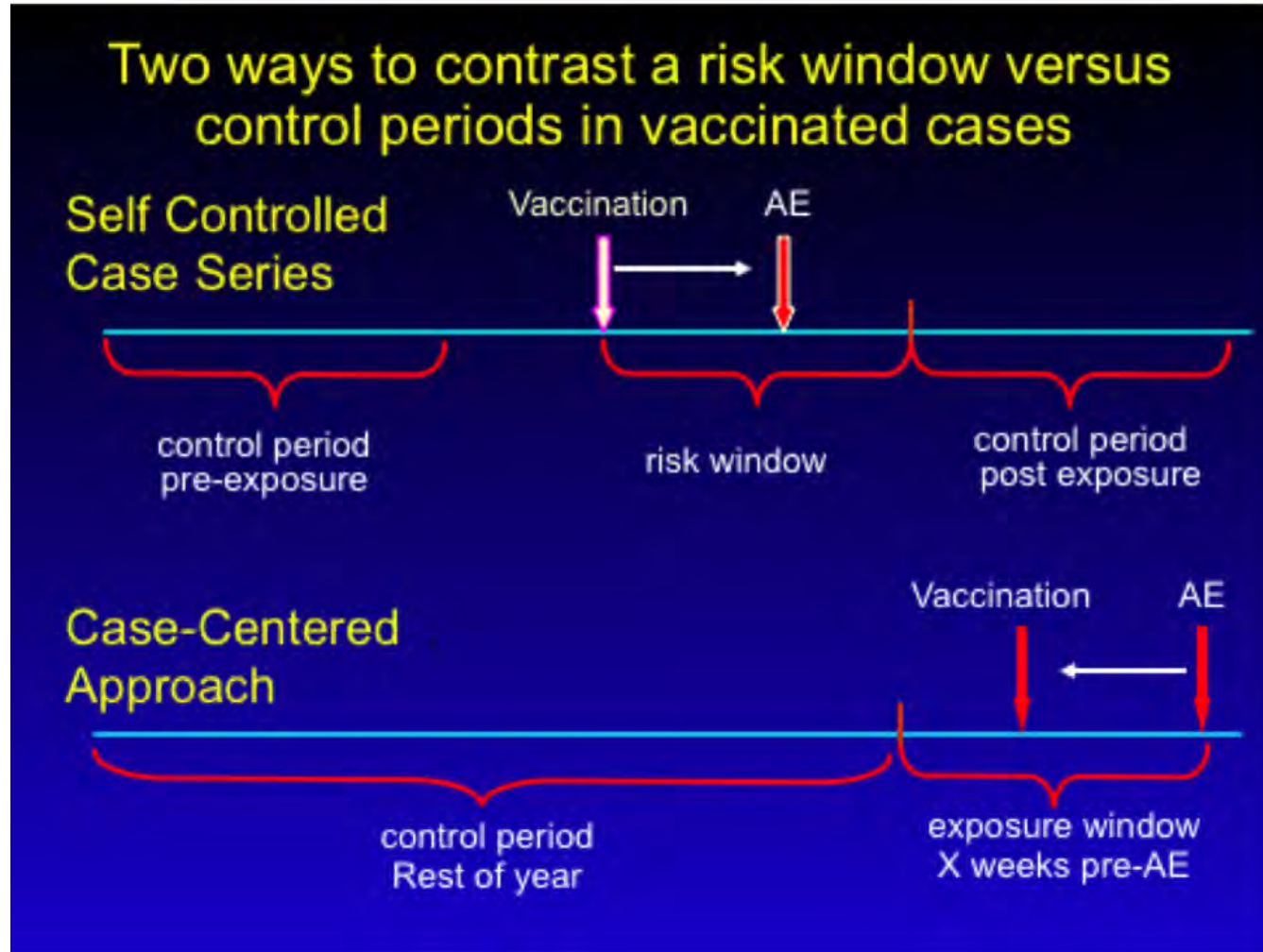
** Quadrivalent human papillomavirus recombinant vaccine. HPV is licensed only for females.

Vaccine Safety Datalink (VSD)

<http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html>

- Large-linked databases, started in 1990
- Links vaccination and health records
- Active ongoing surveillance
 - 9 HMOs
 - ~2% of the U.S. population
- Powerful tool for monitoring vaccine safety
 - Rapid Cycle Analyses
 - Self-controlled Case Series

Self-Controlled & Case-centered Approaches to Analysis of Adverse Events after Immunizations



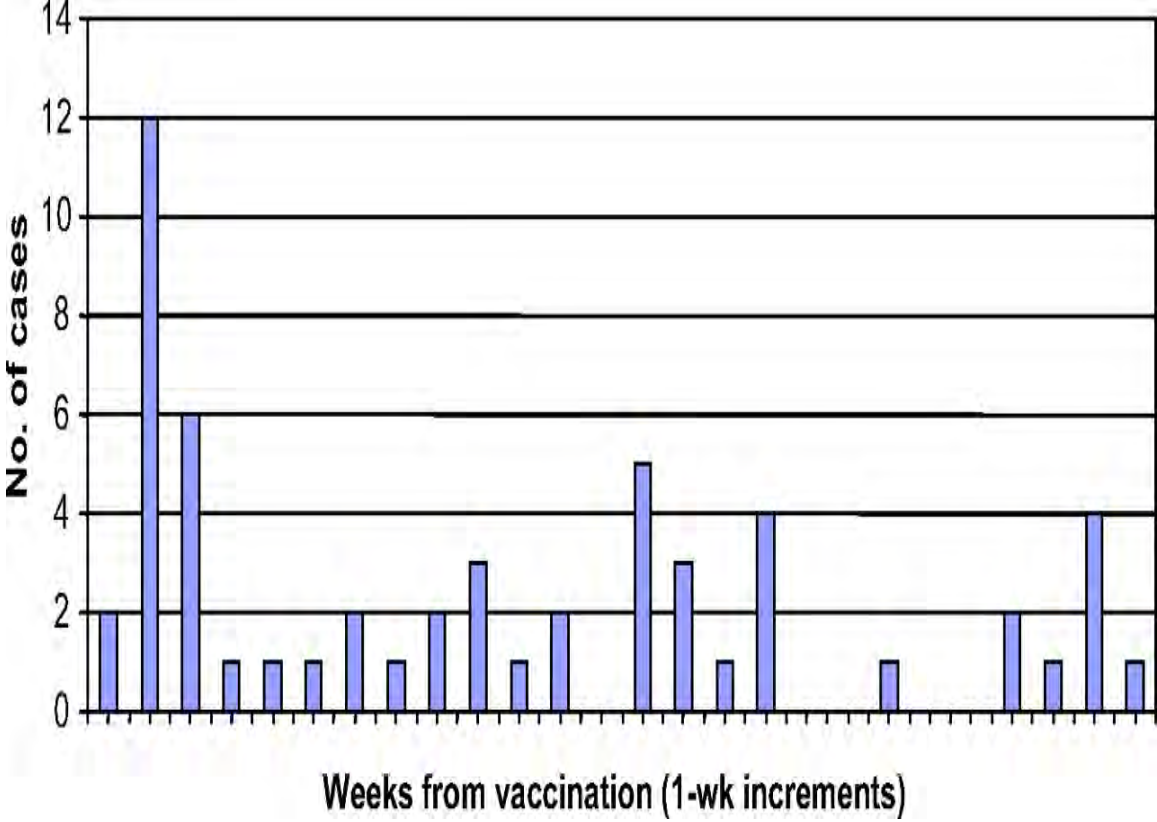
Risk Window Approach:

- Only Vaccinated individuals contribute to the analysis

Case-centered Approach:

- Only Cases contribute to the analysis.
- Each case acts as its own control

Risk of ITP* onset following MMR vaccination



Children 12-23 months

Risk-interval IRR = 3.94
(2.01-7.69)

Self control case series IRR = 5.38
(2.72-10.62)

* Idiopathic Thrombocytopenic Purpura

France, E. K. et al. Pediatrics 2008;121:e687-e692

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Clinical Immunization Safety Assessment (CISA)

- Evaluate persons who experience adverse events temporally associated with immunizations:
 - Referrals → evaluations → recommendations
- Gain better understanding of adverse events:
 - Studies of pathogenesis, genetics, case-control.....
- Develop protocols for healthcare providers:
 - Re-immunization, hypersensitivity testing
- Train Young Investigators to Pursue Careers in Immunization Safety

Examples of CISA Projects

- Retrospective review of the safety of live viral vaccines in patients with DiGeorge Syndrome
- Retrospective review of the safety vaccines in patients with mitochondrial disorders
- Prospective transmission of rotavirus vaccine from healthy vaccinees to immunocompromised household contacts
- Genetics of Guillain-Barré Syndrome in vaccine- and non-vaccine associated case
- Neurologic Adverse events temporally associated with the 2009 H1N1 influenza vaccine
- Adverse events temporally associated with the Pfizer & Moderna mRNA vaccines
 - Anaphylaxis, Bell's palsy, demyelinating disease, death

How Safe is Safe Enough?

TABLE 1. Ratio of number of cases of vaccine-associated paralytic poliomyelitis (VAPP) to number of doses of trivalent OPV* distributed—United States, 1980–1994

Case category	Ratio of number of cases to millions of doses of OPV* distributed and number of cases reported (N) 1980–1994					
	All doses		First doses		Subsequent doses	
→ Recipient	1:6.2	(49)	1:1.4	(40)	1:27.2	(9)
Contact	1:7.6	(40)	1:2.2	(26)	1:17.5	(14)
Community-acquired	1:50.5	(6)	NA		NA	
Immunologically abnormal [†]	1:10.1	(30)	1:5.8	(11)	1:12.9	(19)
Total	1:2.4	(125)	1:0.75	(77)	1:5.1	(42)

* Live, oral poliovirus vaccine (attenuated).

[†] Because the denominator is doses of OPV distributed, the calculated ratio is low. However, if the denominator is the number of immunodeficient infants born each year, the risk for VAPP in immunodeficient infants is 3,200-fold to 6,800-fold greater than in immunocompetent infants [31].

How Safe is Safe Enough?

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.

How Safe is Safe Enough?

January, 1997: ACIP has determined that the *risk-benefit ratio associated with the exclusive use of OPV for routine immunization has changed* because of rapid progress in global polio eradication efforts. In particular, the *relative benefits of OPV to the U.S. population have diminished* because of the elimination of wild-virus–associated poliomyelitis in the Western Hemisphere and the reduced threat of poliovirus importation into the United States. The *risk for vaccine-associated poliomyelitis caused by OPV is now judged less acceptable* because of the diminished risk for wild-virus–associated disease (indigenous or imported). Consequently, ACIP recommends a *transition policy that will increase use of IPV and decrease use of OPV during the next 3–5 years.*

How Safe is Safe Enough?

As of January 1, 2000, ACIP recommends exclusive use of inactivated poliovirus vaccine (IPV) for routine childhood polio vaccination in the United States. All children should receive four doses of IPV at ages 2, 4, and 6–18 months and 4–6 years.Since 1979, the **only indigenous cases of polio reported in the United States have been associated with the use of the live OPV.** Since 1997, the global polio eradication initiative has progressed rapidly, and the **likelihood of poliovirus importation into the United States has decreased** substantially.**No declines in childhood immunization coverage were observed,** despite the need for additional injections.**ACIP reaffirms its support for the global polio eradication initiative and the use of OPV as the only vaccine recommended to eradicate polio from the remaining countries where polio is endemic.**

“The Cow Pock: The Wonderful Effects of the New Inoculation!”



James Gillray, 1802 vide the publication of the Anti Vaccine Society

Typical News Image



DOCTOR-- DONT VACCINES CONTAIN CHICKEN EMBRYOS, EMBALMING FLUID, SPERMICIDES, CANCER-CAUSING AGENTS, GELATIN FROM BUTCHERED ANIMALS, MERCURY, ANTIBIOTICS AND ANTI-FREEZE???

I DONT KNOW-- WE JUST GET PAID TO INJECT AS MANY PEOPLE AS WE CAN!

SOMEONE PLEASE CALL POISON CONTROL!!



COUNTERTHINK



FACT: THE PUSH FOR MANDATORY HPV VACCINES WAS BANKROLLED BY DRUG COMPANIES. TEXAS GOV. RICK PERRY ACCEPTED THOUSANDS FROM MERCK.



TRUST US
VIOXX NOW GARDASIL
TWO GREAT MERCK PRODUCTS



BEWARE OF THE

VACCINazis

New Vaccine Media Coverage

[Jimmy Kimmel, Feb. 2015](#)

BLOG: SPELLS

Vaccinazis preparing mass vaccinations

By **VOODOOBOB**

Posted June 17, 2009 at 9:29 p.m.



"Schoolchildren could be first in line for swine flu vaccine this fall — and schools are being put on notice that they might even be turned into shot clinics.

"Health and Human Services Secretary Kathleen Sebelius said Tuesday she is urging school superintendents around the country to spend the summer preparing for that possibility, if the government goes ahead with mass vaccinations."

<http://www.google.com/hostednews/ap/article/ALeqM5hbs-FO8IE3ZraaOV7CtTQuSuaVigD98S0U402>



This is out of control. This flu strain has killed 160 people worldwide, which is far less than a typical flu season. And what else will be in the shots? If they come in bulk multidose vials they'll probably have thimerosal (mercury) in the usual dose

<http://www.vaccinesafety.edu/thi-table.htm>



because this so-called "government" STILL hasn't seen fit to protect american children from injected mercury, even though the proof of its connection to autism was published in 2005:

<http://www.sciencenews.org/articles/20050416/note14.asp>



It's not like there aren't alternatives. Europe outlawed mercury vaccine preservatives years ago.

Just exactly what are we buying with our federal tax dollars?



What kind of government would deliberately destroy children's lives?

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Recent Case of Child with Autism, Mitochondrial Dysfunction

J. Child Neurology. Poling, 2006

- 19 month old female, well until 48 hrs post-immunization (DPT, HIB, MMR, Polio & Varicella):
 - T=38.9° C, inconsolable crying, irritability, lethargy, refusal to walk
 - 4 days later: waking up multiple times in the night, episodes of opisthotonos*, and no longer normally climb stairs
 - Low-grade intermittent fever for the next 12 days
 - 10 days post-immunization: generalized erythematous macular rash

* condition in which a person holds their body rigid and arches their back, with their head thrown backward.

Recent Case of Child with Autism, Mitochondrial Dysfunction

J. Child Neurology. Poling, 2006

- **23 months:** Childhood Autism Rating Scale score 33 (mild autism range)
- Persistent mild lactic acidosis, ↑CK, AST → Muscle biopsy
 - **Abnormal histology:** type I myofiber atrophy, increased myofiber lipid content, reduced cytochrome *c oxidase activity*.
 - **Oxidative phosphorylation enzymology:** reduced complex I, I + III, and III activity. Complex IV activity near the 5% confidence limit of the control group.
 - **Mitochondrial DNA sequencing:** normal
- **Gradual Improvement:**
 - **6 yrs of age:** attends kindergarten with an Aide
 - Autism score <30

• Popular media reported:

-this was the first time that the U.S. government conceded that vaccines cause autism

[David Kirby: Government Concedes Vaccine-Autism Case in Federal ...](#)

Feb 25, 2008 ... 3) If the **government** is claiming that **vaccines** did not "**cause**" autism, ... (Coincidentally, the **first** case of Mt disease was diagnosed in 1959, just 15 years ... **Vaccine War: Autism, Flu and Science - Wellness - TIME.com** ...
www.huffingtonpost.com/.../government-concedes-vacci_b_88323.html - **Cached** - **Similar**

[Government Again Concedes Vaccines Cause Autism - My World of ...](#)

Feb 25, 2009 ... **Government Again Concedes Vaccines Cause Autism** ... messages by telling the world that vaccines don't cause autism, while, at the same **time**, ... Although the **US** vaccine court continues official denials of any connection ... Zeller was one of the **first** to prove his case in the Federal Vaccine Court. ...
floridablocks.blogspot.com/.../government-again-concedes-vaccines.html - **Cached** - **Similar**

[Government Concedes Vaccine-Autism Case in Federal Court - Now ...](#)

Oct 26, 2009 ... 3) If the **government** is claiming that **vaccines** did not "**cause**" autism, ... at the **time** of vaccination, but nobody detected, or even suspected it. ... just 15 years after the **first** autism case was named, ... 2 Responses for "**FLASHBACK: Government Concedes Vaccine-Autism Case in Federal Court**" ...
www.puppetgov.com/.../flashback-government-concedes-vaccine-autism-case-in-federal-court-now-what/ - **Cached**

[NeuroLogica Blog » Has the Government Conceded Vaccines Cause Autism?](#)

Feb 29, 2008 ... But the **US** **government** did not admit **vaccines** cause autism – they This is especially critical given the **time** lag between the **first** ...
theness.com/neurologicablog/?p=203 - **Cached**

[Government Concedes Vaccine-Autism Case in Federal Court - Now What?](#)

Feb 25, 2008 ... 3) If the **government** is claiming that **vaccines** did not "**cause**" ... may have had Mt disorder at the **time** of vaccination, but nobody detected, or even suspected it. ... just 15 years after the **first** autism case was named, ...
www.organicconsumers.org/articles/article_10655.cfm - **Cached** - **Similar**

[Government Again Concedes Vaccines Cause Autism - AGE OF AUTISM](#)

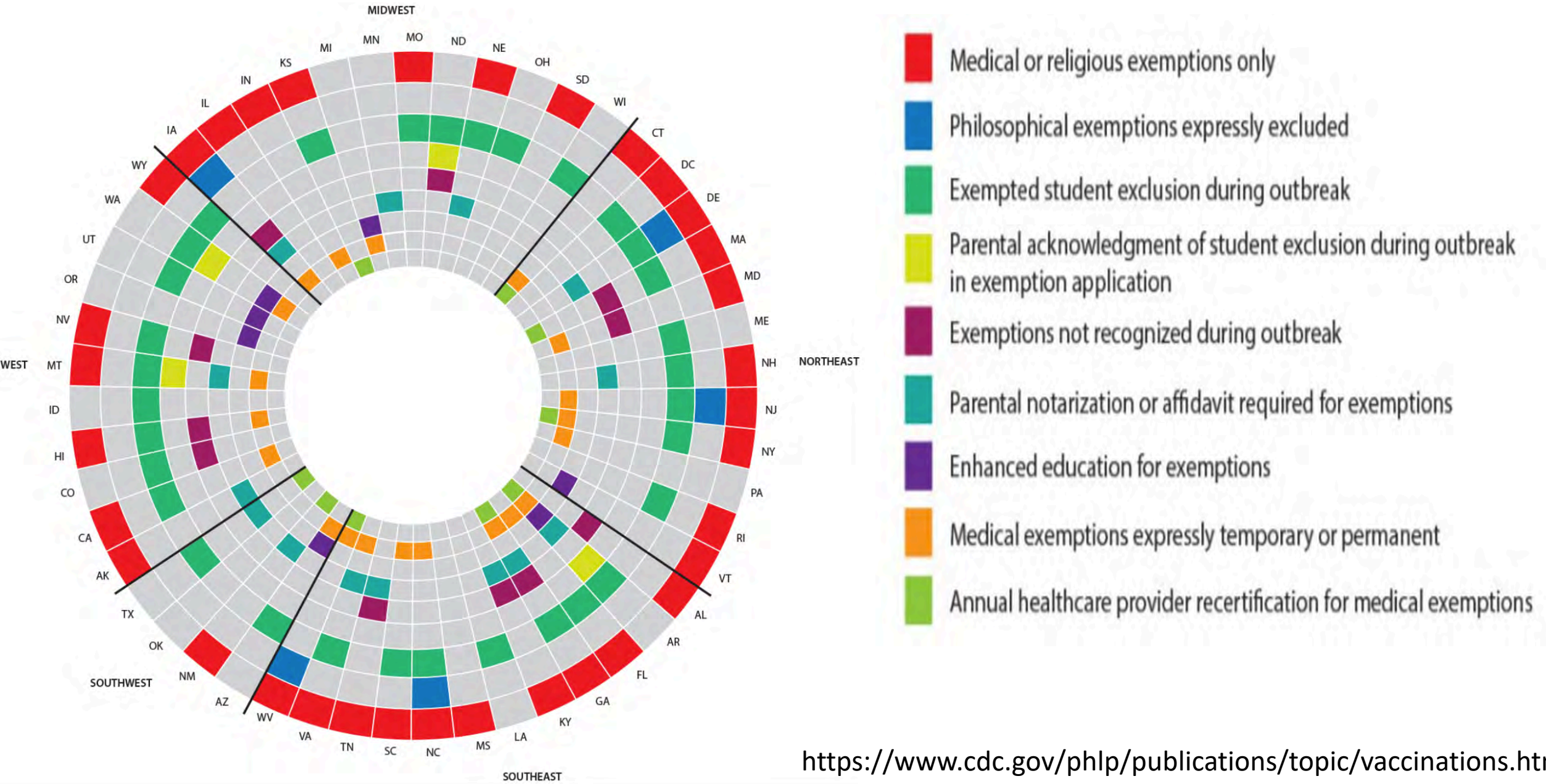
Feb 25, 2009 ... The **first** was the case of Hannah Poling in March of 2008, where the ... reacted to the news, "It seems the **U.S. government** is sending mixed messages by telling the world that **vaccines** don't **cause** autism, while, at the same **time**, ... **Vaccines** cause brain damage which is being labeled as **autism** to ...
www.ageofautism.com/.../government-again-concedes-vaccines-cause-autism.html - **Cached** - **Similar**

[Outlaw Forum :: View topic - Government Concedes Vaccine-Autism ...](#)

19 posts - 11 authors - Last post: Mar 5, 2010
Would the **government** be obliged to **concede** 500, or even 1000 cases? But I doubt **mercury vaccines** causes **autism**. ...
www.outlawjournalism.com/forum/viewtopic.php?t=1031&sid...

- **What the Division of Vaccine Injury Compensation said was:**
 - “..... the facts of this case meet the statutory criteria for demonstrating that the vaccinations CHILD received on July 19, 2000, significantly aggravated an underlying mitochondrial disorder, which predisposed her to deficits in cellular energy metabolism, and manifested as a regressive encephalopathy with features of autism spectrum disorder. Therefore, respondent recommends that compensation be awarded to petitioners in accordance with 42 U.S.C. § 300aa-11(c)(1)(C)(ii).”
(<http://huffingtonpost.com, 2007>)

State School Vaccination Exemptions Law



National Vaccine Injury Compensation Program

<http://www.hrsa.gov/vaccinecompensation/>

- Enacted in 1986
 - Went into effect in 1988
 - Amended in 1989.....
- “no-fault” alternative to the traditional tort system for resolving certain vaccine injury claims
 - Petitioners must file with NVICP prior to filing suit in the courts
- Original Vaccines covered:
 - diphtheria, tetanus, pertussis, measles, mumps, rubella, and polio.

Vaccine Injury Compensation Trust Fund

- **Funds the National Vaccine Injury Compensation Program (VICP) to compensate vaccine-related injury or death claims for covered vaccines administered on or after October 1, 1988.**
- **\$0.75 excise tax on each dose of vaccine purchased:**
 - Tax on a dose of trivalent influenza vaccine is \$0.75 because it prevents one disease
 - Tax on a dose of MMR is \$2.25 because prevents three diseases.
- **Taxable vaccines are those recommended by the CDC for routine administration to children.**
- **Dept. of Treasury collects the excise taxes, oversees and manages the investing activities for the Trust Fund.**
- **January 31, 2014, the balance was nearly \$5.7 billion.**

Review of Adverse Effects of Vaccines

- HRSA contracts with Institute of Medicine (IOM) to review evidence regarding adverse health events associated with vaccines covered by the Vaccine Injury Compensation Program.
- <http://www.hrsa.gov/vaccinecompensation/vaccinetable.html>

National Childhood Vaccine Injury Act, Vaccine Injury Table

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
I. Vaccines containing tetanus toxoid (e.g., DTaP, DTP, DT, Td, or TT)	A. Anaphylaxis or anaphylactic shock	4 hours.
	B. Brachial Neuritis	2-28 days.
	C. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable.
II. Vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis bacteria, or specific pertussis antigen(s) (e.g., DTP, DTaP, P, DTP-Hib)	A. Anaphylaxis or anaphylactic shock	4 hours.
	B. Encephalopathy (or encephalitis)	72 hours.
	C. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable.
III. Measles, mumps, and rubella vaccine or any of its components (e.g., MMR, MR, M, R)	A. Anaphylaxis or anaphylactic shock	4 hours.
	B. Encephalopathy (or encephalitis)	5-15 days (not less than 5 days and not more than 15 days).
	C. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above	Not applicable.

Adverse Event

- Any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related (21 CFR 314.80)
 - sign, symptom, or disease
 - abnormal lab, VS, imaging, ECG, etc. – worsening of the above – constellation of the above ideally, prospectively established case definition (e.g., drug induced parkinsonism)

AE Severity Grading Scale (FDA/CBER)

- **Healthy adult and adolescent volunteers** in vaccine trials:
 - Grade 1 Mild
 - Grade 2 Moderate
 - Grade 3 Severe
 - Grade 4 Potentially Life-threatening

Serious Adverse Event (21 CFR 312.32(a))

- **Any adverse event that results in the opinion of the Investigator or Sponsor in:**
 - **Death, or is life-threatening** (immediate risk of death)
 - **Hospitalization**, or prolongation of existing hospitalization
 - Persistent, or significant **incapacity**, or substantial disruption of the ability to conduct normal life functions (AKA disability)
 - **Congenital anomaly / birth defect**

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia				Insulin requirements or hyperosmolar coma
Fasting – mg/dL	100 – 110	111 – 125	>125	
Random – mg/dL	110 – 125	126 – 200	>200	
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN” is the upper limit of the normal range.

Vaccine hesitancy, and refusal

- Refusal of routine childhood immunizations, **Pakistan** (Int J Infect Dis 104; 2021; 117-24)
 - **27.9% of parents refused vaccination** of their children.
 - the majority of mothers had no education (85.3%); $p = 0.03$], were less likely to own a mobile phone than fathers [24 (14.1%) vs 152 (89.4%); $p = 0.001$].
 - The vaccination refusal rate was higher in parents with food security [$n = 88$ (51.8%)] compared with parents with minimal food insecurity [$n = 62$ (36.5%)] and high food insecurity [20 (11.8%); $p = 0.05$].
 - The majority who refused [$n = 103$ (60.6%); $p = 0.005$] believed that **vaccination has serious adverse effects**. As a result, 19.4% of parents disagreed with doctors' recommendations to vaccinate their children.
 - **Over half of parents (50.6%) disagreed with the statement that vaccination can protect children**
- Socioeconomic Determinants in Vaccine Hesitancy and Vaccine Refusal in **Italy** (Vaccines 2020, 8, 276; doi:10.3390/vaccines8020276)
 - On the basis of self-reported vaccination status, timeliness of vaccinations, and intention, families were classified as provaccine (64%), hesitant (32.4%), or antivaccine (3.6%):
 - Rising levels of **perceived economic hardship** were associated with hesitancy (AOR from 1.34 to 1.59), and **lower parental education** was significantly associated with refusal (AOR from 1.89 to 3.39).

U.S.A.

- Families who reject the standard vaccine schedule fall into 2 groups.
 - **Vaccine hesitant parents** may delay or space out vaccines or accept specific vaccines only. In a 2011 survey, **13% of US parents** with children younger than 6 years fall into this group.
 - **Parents who accept no vaccines** for their children fall instead into the vaccine refusal category. In 2017, **1.3%** of US toddlers were fully unvaccinated, which has more than doubled in the past 20 years.
 - **The parents of fully unvaccinated children** tend to be **white, higher income, and more educated**; these families often have full access to vaccines but choose to refuse them.
 - **Reasons cited:** autism, thimerosal (removed from US vaccines in 2001), multiple vaccines overloading the immune system

Safety Issues to consider when you present your vaccine

- **Outline your preliminary safety testing strategy for a phase 2b clinical trial. Include the following safety issues:**
 - Expected safety issues based on your vaccine format
 - Antibody Dependent Enhancement (ADE)
 - Effect of prior disease, or vector immunity
 - Mechanism(s) for capturing unexpected safety issues
- **Outline approaches for testing and/or capturing safety issues in special populations, even if they are not part of your clinical trial:**
 - Immunodeficient subjects, Children, Very Elderly (75plus)
- **Describe how, and in what clinical setting(s) you are going to monitor safety issues**
- **Estimate frequency of Serious Adverse Events, and resulting sample size needs**

Efficacy Issues to consider when you present your vaccine

- **Outline your primary and secondary efficacy/outcome measures** for a phase 2b trial, include the following:
 - **Case definitions** for Infection, and/or clinical disease
 - Describe your **case adjudication process**
 - **Describe how, and in what clinical setting(s)** you are going to test efficacy/ outcomes
 - **Estimate projected efficacy, and resulting sample size needs**

Questions?