

Safety & Efficacy Testing

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Course Number PB-VI01P: Development of a Vaccine During a Pandemic
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Topics for Discussion

- **Goals of an immunization program:**
 - **Role of epidemiological data in developing and monitoring immunization strategy:**
 - Active & Passive surveillance programs
 - Influenza, Varicella, Polio
 - Eradication vs. limitation
 - Universal vs. targeted immunization
 - Other tools for use in conjunction with immunizations
 - Passive protection, therapeutic agents, cohorting & quarantine
 - **How do you measure efficacy?**
 - Disease prevention
 - Surrogate markers
 - Phase I, II, III & IV studies
 - What type of study design is preferred: cohort, case-control, ecological?

Role of epidemiological data in developing and monitoring immunization effectiveness & safety

- **Passive surveillance programs:**

- Standardized report forms available from state/ local DOHs which are returned when cases are detected & reported by practitioners.

- **Benefits:**

- Less costly than active reporting systems

- Data collection is not burdensome to health officials

- Data can be used to identify trends or outbreaks if reporting is robust

Passive Surveillance Programs

- **Limitations:**

- Non-reporting/under-reporting → ↓ representativeness of the data, → undetected trends/outbreaks, inappropriate conclusions

- **Reasons for not reporting:**

- Lack of awareness of reporting requirements by health care providers
- Perception by health care providers that nothing will be done with the data
- Lack of interest, burdensome reporting forms, etc.
- Case definitions that are unclear, recently changed, or changes in reporting requirements
- Hardware/software systems that cannot capture the necessary information in databases
- Stigmatization associated with the disease to be reported (i.e. STDs)
- Patient is not willing to provide necessary information

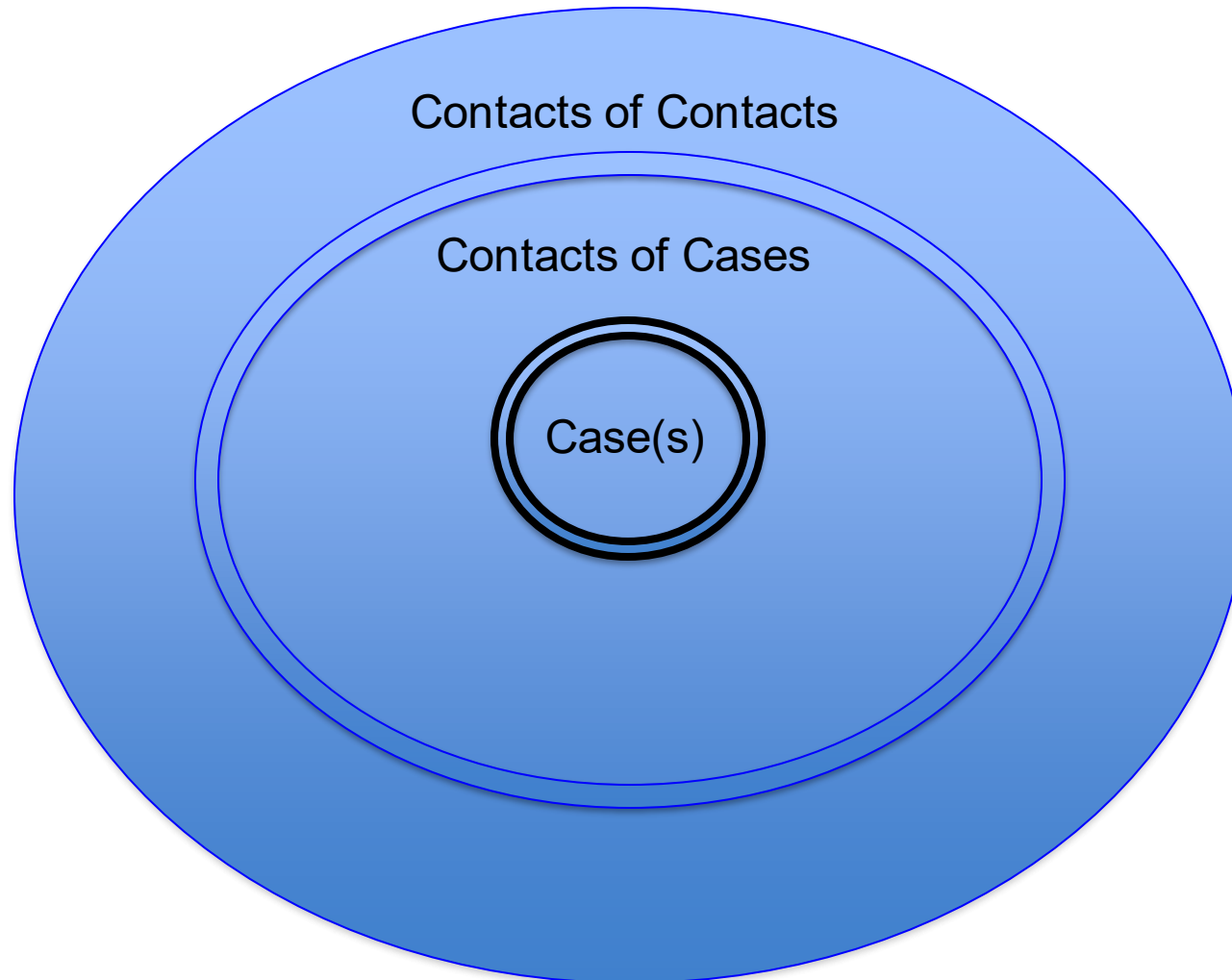
Active Surveillance Programs

- **Outreach by Public Health Officials, or their designates:**
 - Regular telephone calls/visits to labs, hospitals, providers
 - Elicit/verify case reports and/or review medical records, lab reports and other alternative sources
 - Regular data transfers (e.g. hospitals/ clinic data to NYC Immunization Registry)
 - Identify cases that may not have been reported by passive surveillance systems

Active Surveillance Programs

- **Benefit: improved & more complete reporting**
 - Rationale for Active Surveillance:
 - Conditions of particular importance
 - Document a suspected outbreak
 - Augment timely disease intervention or epidemiologic investigation (congenital syphilis, intrapartum Hepatitis b)
 - Validation of representativeness of passive reports
 - Enhance accuracy, completeness, and timeliness of reporting
 - Assess impact of immunization programs
 - Vaccine preventable diseases targeted for eradication (smallpox):
 - Reassess strategy: mass immunization → targeted ring immunization
- **Limitation: much higher costs**

Smallpox Vaccine “Ring” Strategy: Surveillance & Containment



- 1. Find & isolate** case(s)
- 2. Identify & vaccinate** contacts of case(s) within days of exposure
- 3. Identify & vaccinate contacts of contacts** within days of exposure

How Do You Evaluate Surveillance Programs?

- 1988, Pan American Health Organization as part of the polio eradication effort:
- **Required surveillance indicators**
 - **Measures of surveillance infrastructure**
 - Number of reporting units reporting on a weekly basis
 - **Timeliness of notification**
 - The interval between case onset and notification
 - **Adequacy of case investigation**
 - The proportion of cases with appropriate lab specimens
 - **Timeliness of laboratory testing**

Polio

- Active surveillance for acute flaccid paralysis (AFP)
- Lab testing for confirmation of wild-type & vaccine-associated polio isolates
- **Protocol:**
 - **Identify cases clinically consistent** with polio (suspected cases)
 - High sensitivity, lower specificity
 - **Track suspected cases** until lab either confirms or rules out wild-type poliovirus
 - May be performed on only a subset of all cases of AFP
 - **If adequate laboratory testing was not obtained**, the case was classified as “compatible” and considered a failure of case investigation and surveillance

Specific Examples: Polio

- In the absence of polio, other causes of AFP in children occur at a fairly constant rate over time:
 - Allows monitoring of the adequacy of ascertainment of suspected cases of polio by tracking the **incidence of AFP among children <15 yrs.**
 - In countries/ regions reporting rates of AFP $\geq 1/100,000$ children <15 yrs and without confirmed/compatible cases of polio → confidence that the absence of reported cases of polio means the absence of polio.
 - However, if AFP rates were $< 1/100,000$ among children <15 yrs , the absence of cases could mean inadequate surveillance rather than the absence of polio.

How Do You Confirm That The Absence of Reported cases = Absence of Disease?

- **External Standards:**
 - Detect cases of non-polio AFP
 - Detect non-type b H. influenzae in invasive disease (bacteremia & meningitis) in kids < 5 years
- **Identification of Imported Cases**
 - Measles, Polio & Congenital rubella
- **Monitor level of reporting of suspected cases that are eventually ruled out**
 - ↓ utility when disease of interest disappears
- **Monitor the diagnostic effort**
 - Track the number of samples submitted for testing over time
- **Monitor circulation of the organism**
 - Use molecular techniques for surveillance/ rubella, pertussis...

Influenza

Goals of the current surveillance program

- Find out when & where influenza activity is occurring
- Track influenza-related illness
- Determine what influenza viruses are circulating
- Detect changes in influenza viruses
- Measure the impact that influenza & vaccine is having on hospitalizations and deaths

Influenza

- **Categories of Surveillance**
 - **Viral Surveillance:** 80 W.H.O. & 60 National Respiratory and Enteric Virus Surveillance System (NREVSS) labs in the U.S.
 - All state & some county Public Health labs & some large tertiary care/academic medical centers
 - # of respiratory samples tested, # positive for influenza A & B, some report subtyping (A/H1N1 vs. A/H3N2), patient age
 - Further subtyping (A/H1N1 vs. A/2009 H1N1), antiviral resistance, sequencing, etc. carried out at the CDC
 - **U.S. Outpatient Influenza-like Illness (I.L.I.):**
 - <http://www.cdc.gov/flu/weekly/fluviewinteractive.htm>
 - ILI defined as **fever + cough and/or sore throat** in the absence of a **KNOWN** cause other than influenza
 - > 3,000 healthcare providers in all 50 states, the District of Columbia and the U.S. Virgin Islands reporting over 25 million patient visits each year.
 - Each week, approximately 1,800 outpatient care sites report to CDC
 - the total number of patients seen
 - the number of those patients with influenza-like illness (ILI) by age

Influenza

- **Categories of Surveillance**
 - **Mortality Surveillance**
 - **122 Cities Mortality Reporting System** — each week, the vital statistics offices of 122 cities across the U.S. report total number of death certificates received & the number for which pneumonia or influenza was listed as the underlying or contributing cause of death by age group
 - **Influenza-Associated Pediatric Mortality Surveillance System:** Any lab-confirmed influenza-associated death in a child < 18yrs.
 - **Hospitalization Surveillance**
 - Influenza Hospitalization Network (FluSurv-NET)
 - Aggregate Hospitalization and Death Reporting Activity (AHDRA)
 - **Summary of the Geographic Spread of Influenza**

How Do You Measure Vaccine Efficacy?

- Pre-licensure Phase I, II, III studies
- Disease prevention:
 - pathogen specific 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?

Definitions

- **Vaccine coverage:**

- The percentage of persons that have received a vaccine among all individuals in a particular group who are eligible to receive the vaccine

- **Vaccine efficacy:**

- The ability of a vaccine to provide protection against disease under ideal circumstances (i.e. during a clinical trial)

- **Vaccine effectiveness:**

- The ability of a vaccine to provide protection against disease when used under field conditions (i.e. as used in routine practice)
- = $1 - (\% \text{ disease in vaccinees}) / (\% \text{ disease in unvaccinated vaccine eligible controls})$

Vaccine Clinical Trials

- **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**
- **Determine 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:**

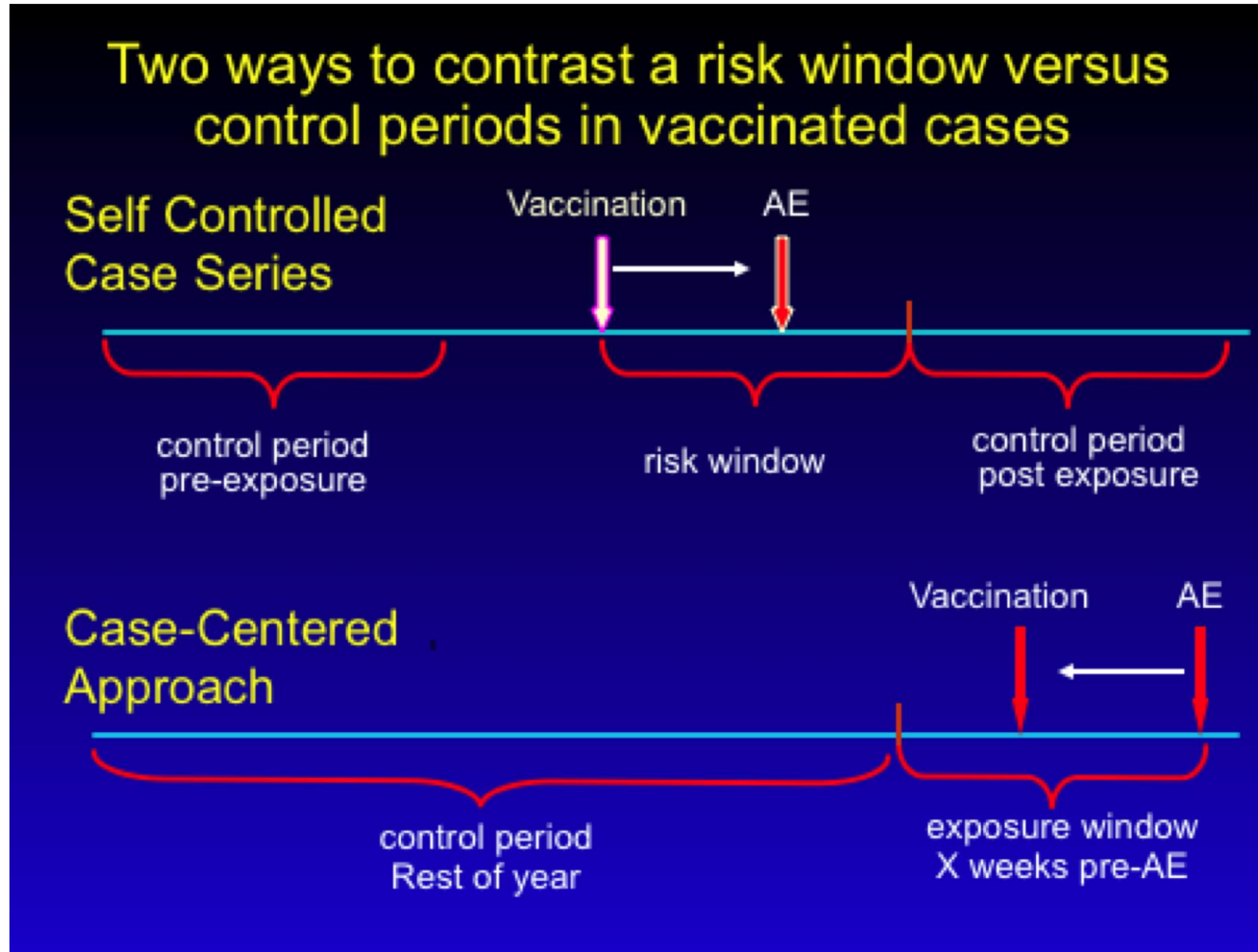
- Varicella vaccine effectiveness

- 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

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

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
 - **FDA approval for specific indications warranted by the Clinical Trials data**
 - **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?

Federal Government's Role

- **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

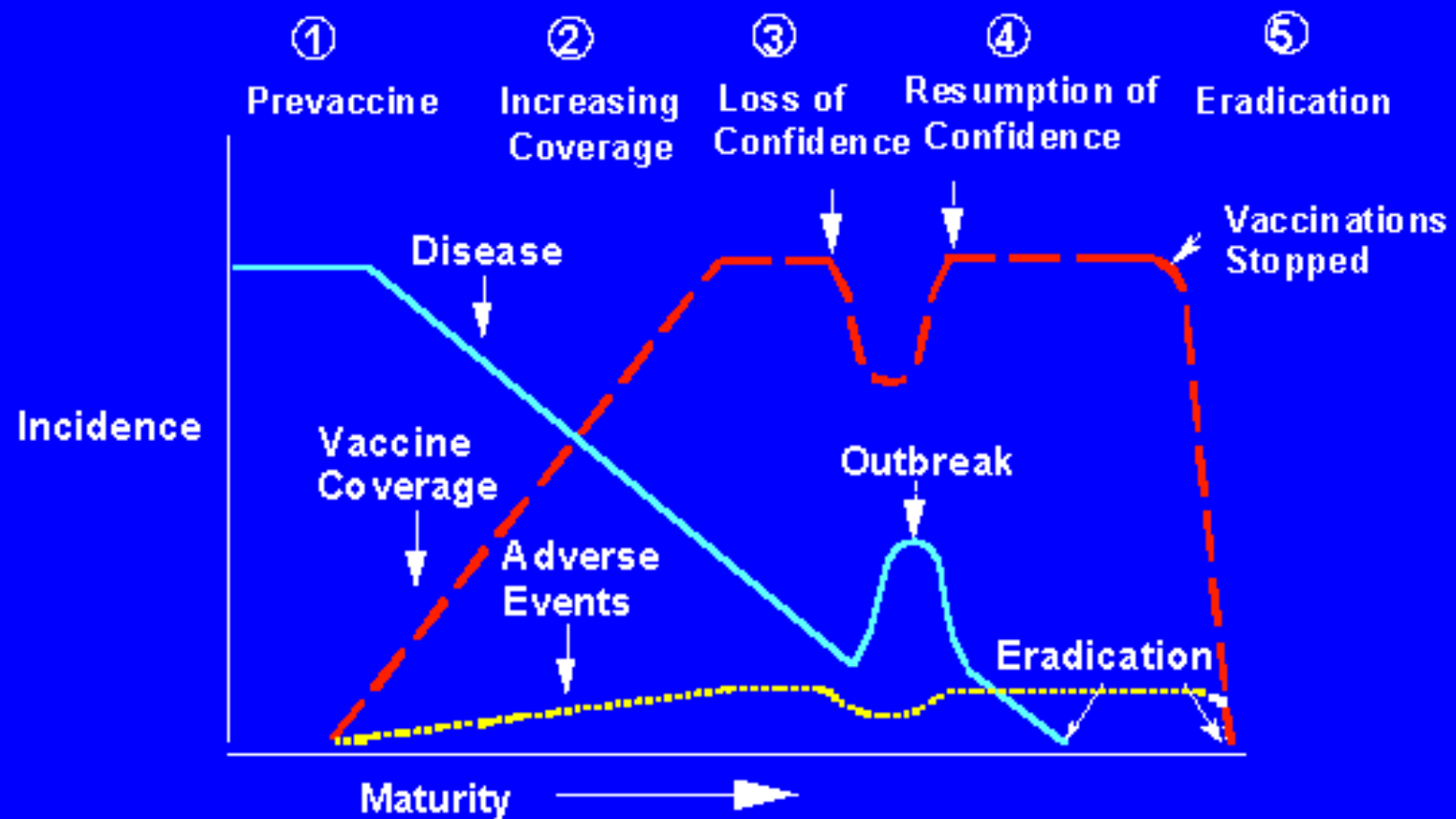
Immunization Safety Issues

- How do we evaluate immunization safety?
- How safe is safe enough?
- Public perception vs. scientifically collected data
- Role of the media

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



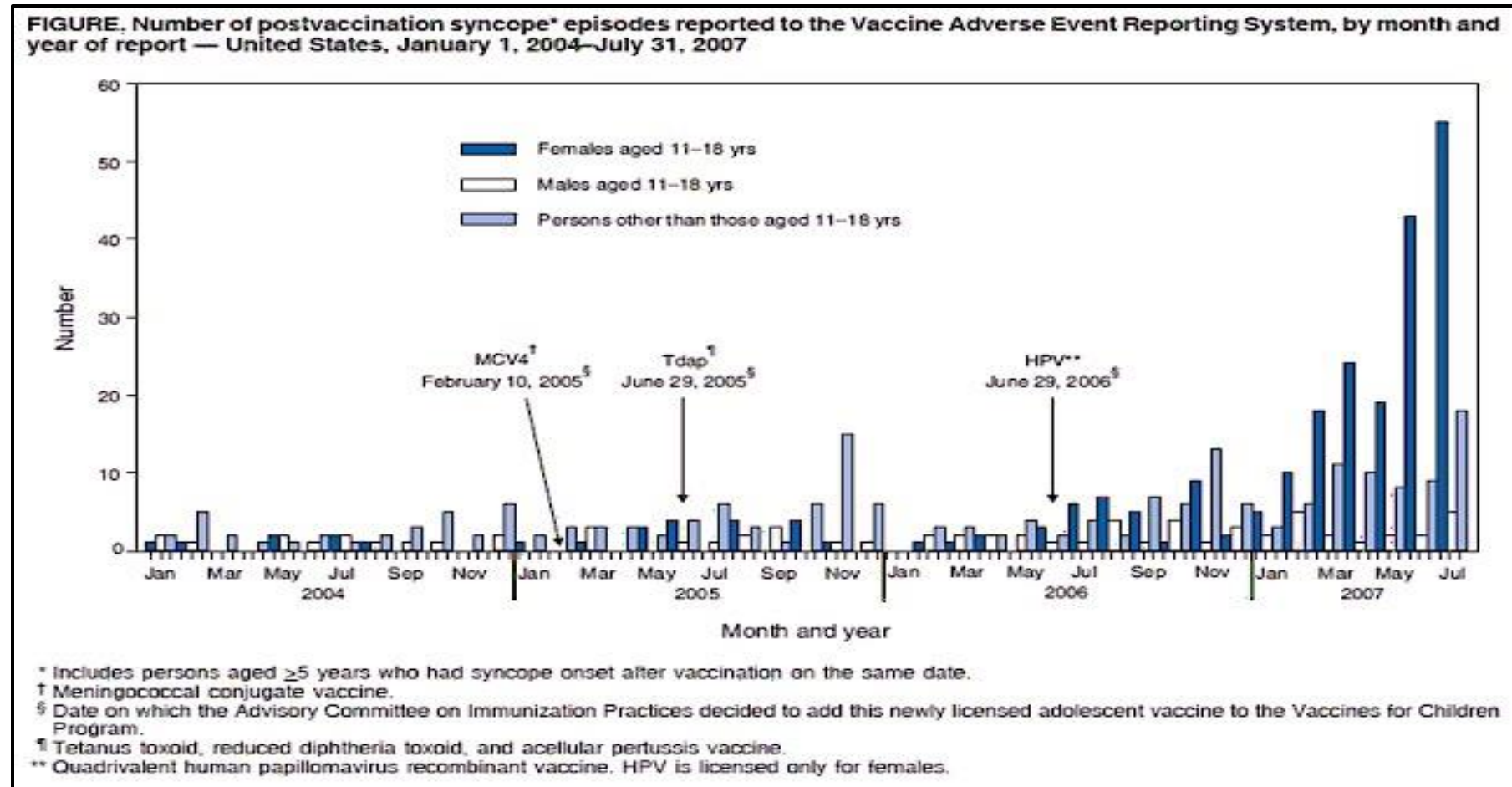
Post-Licensure Vaccine Safety Activities

- **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



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

Clinical Immunization Safety Assessment (CISA)

- Evaluate persons who experience adverse events temporally associated with immunizations:
 - Referrals ⑨evaluations ⑨ecommendations
- 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

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.**

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>

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**

Your Assignment: Safety

- **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**

Your Assignment: Efficacy

- **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**