Vaccine Safety

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Learning Objectives

- Upon conclusion of this session, participants will be able to
  - Describe **how** we know vaccines are safe
  - Relate **what** is done to keep vaccines safe
  - List what each of us can do to **assure** vaccine safety going forward

Rationale for the Learning Objectives

- Vaccine safety a top concern among the vaccine hesitant
- Vaccine hesitancy is persistent and worsening
- Trust in routine vaccination is eroding
- This problems calls for **trusted messengers**
- You are by your roles trusted messengers
- Trusted messengers need to understand vaccine safety thoroughly

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Rationale for the Vaccine Safety

- Vaccines are given routinely to healthy individuals
- Given the goal to prevent illness, we have a **higher standard**
- Vaccines must be far safer than drugs and other medical therapies

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Vaccine Safety as a Concept

- We distinguish **reactivity** from safety
- Both concern adverse events
- Reactivity refers to brief adverse effects that resolve completely
- Safety refers to permanent illness or injury leading to disability

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Examples of Reactivity

- **Local** reactions
  - Redness
  - Swelling
  - Tenderness
  - Pain
  - Induration
- **Systemic** reactions
  - Fever
  - Headache
  - Malaise
  - Irritability
  - Lethargy
  - Fatigue
  - Generalized rash

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What Is Done to Make Vaccines **Less Reactive**

- Refinements in the active agent
  - Move from whole cell pertussis to acellular pertussis
    - DTaP not DTwP
  - Reduced dose
    - Tdap for those 7 years and older
  - Restricted use
    - MMRV only after discussion for first dose MMR and VAR
  - Split virion product rather than whole virion product with influenza

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What We Mean by Vaccine Safety

- Reactivity refers to brief adverse effects that resolve completely
  - Common
  - Mild to moderate
  - Resolves completely
- Safety refers to illness or injury that can lead to **disability or worse**
  - Rare
  - Moderate to severe
  - Prolonged
  - Can be life-threatening

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Examples of Vaccine Safety Concerns

- Serious allergic reactions or anaphylaxis
  - Two or more organ systems affected by IgE mediated allergic response
  - Can be life threatening
  - Typically appears in the first 15 minutes of receipt
- Thrombocytopenia or low platelets
- Occurrence of Guillain-Barre Syndrome
- In case of live vaccine, vaccine-associated infection, contagion
- Shoulder injury related to vaccine administration
- Presyncope and syncope

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What Is Being Done to Make Sure Vaccines are Safe

- Food & Drug Administration or FDA licensure
- Adherence to schedule, ages & intervals, contraindications
- Required post-licensure study
- Adverse events reporting
- Adverse events investigations

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FDA Licensure

- Preclinical studies
  - Lab bench
  - Animals
  - Lot-to-lot consistency
- **Prelicensure** clinical trials in human volunteers
  - Phase 1 with dozens of volunteers
  - Phase 2 with hundreds of volunteers
  - Phase 3 with tens of thousands of volunteers
- Postlicensure clinical studies
  - Phase 4 required studies

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Phase 1 Experimental Trials

- Goal is to find the **right dose**
- Strongest acceptable dose
- 20 to 100 healthy volunteers
- Often 3 volunteers a dose
- Starting with very small dose
- Dose-limiting reactivity
  - Systemic symptoms like fever
  - Local signs like injection site inflammation

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Phase 2 Experimental Trials

- Goal is to assess immune response and safety
- **Several hundred volunteers**
- All get experimental vaccine at dose found in Phase 1
- Ages/conditions match the target age of those to be vaccinated
- Testing schedule of doses thought to be effective
- Immune system response
- Safety and reactivity
- If FDA approves, then can move to Phase 3

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Phase 3 Experimental Trials

- **Pivotal** trials upon which licensure depends
  - With vaccines in thousands of volunteers
  - With drugs usually just hundreds
- In ages when vaccine is to be given
- Along with other vaccines due at those ages
- Given at schedule found most immunogenic in Phase 2 trials
- Always randomized, controlled trials
- Always protocol registered (“locked in”) before first volunteer starts
- Double-blinded to reduce risk of bias

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Details with Phase 3 Experimental Trials

- Randomized to either active agent (vaccine) or control (e.g. placebo)
- Controls usually consist of saline or vaccine vehicle minus active agent
- Requires **adequate follow-up time** to be exposed to infectious agent
  - Months or years following vaccine completion
  - Post vaccination follow-up for disease detection
- Measures efficacy (disease prevention as compared to control)
- Measures reactivity versus control
- Detects adverse events in an even larger population than Phase 2

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Results of Phase 3 Trial Testing

- If Phase 3 trial(s) successful, manufacturer can get licensure
- This is why Phase 3 trials are called **pivotal** trials
- If successful, manufacturer can license and sell product
- If failure, no future for product; already studied it at highest dose

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The Meaning of that FDA Licensure

- Only **that manufacturer** can make the product
- Only use licensed is the use in the Phase 3 testing
  - Dosing
  - Route
  - Age
  - Indication
- Only the same manufacturing process and materials can be used
- FDA monitors manufacture, lot to lot consistency, and safety
- FDA may require manufacturer to do post-licensure Phase 4 tests

Next Step is ACIP Recommendation

- Many FDA licensed vaccines are not ACIP-recommended
- ACIP stands for Advisory Committee on Immunization Practice
- US Advisory Committee
- 15 voting members, 14 experts, 1 layperson
- Meets three times a year open to public and public comment
- Hosted by CDC, supported by FDA
- **Only federal source** of civilian vaccine recommendations

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Basis for ACIP Recommendation

- Evaluates data submitted to the FDA for efficacy, safety
- Evaluates epidemiologic data obtained by CDC
- Evaluates other peer-reviewed studies
- Grades the evidence
- Makes recommendation based on **4 criteria**
  - Safe
  - Efficacious
  - Necessary
  - No alternative

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ACIP Recommendation Contents

- Indication: who should get it
  - Age
  - Catch-up
  - Risk-based use
- Contraindications: who should not get it
- Precautions: who might get it with consideration
- May **veer** from FDA licensure
- Produces annual schedule of all vaccines
- Creates VISs

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Of Note, the ACIP May **Reduce** Doses or Eliminate Vaccines

- Dosing of HPV vaccine for healthy children 9 through 14 years
  - Two doses 6-12 months apart
  - Not three doses at 0, 1-2, and 6 months
- Dosing of rabies vaccination post-exposure
  - Four doses at Days 0, 3, 7 and 14
  - Not five doses at Days 0, 3, 7, and 28
- Prevnar-13 pneumococcal vaccine for those 65 years and older
  - Routine recommendation ended given disappearance of disease

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ACIP May Also Approve Brand **Interchangeability**

- Completion of a series with alternative brand
  - E.g., Menveo and Menquadfi
- Complete of series with alternate route
  - E.g., injected Fluarix and nasal spray Flumist

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Vaccine Information Statements or VISs

- Created for routine vaccines
- **Required** by federal law to be given before each dose
- Contains highly readable text explaining the following
  - Who should get vaccine
  - Who should NOT get vaccine
  - What are typical reactions
  - How to report adverse events

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Post-Licensure Monitoring

- FDA monitors closely ongoing production
- FDA allows no change in ingredients
- FDA allows no change in manufacturing process
- FDA requires batch-to-batch consistency

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Post-Licensure **Studies**

- FDA may also require manufacturer to conduct Phase 4 studies
- Types
  - Case-controls
  - Prospective cohort studies
  - Additional randomized controlled trials

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Limits of Prelicensure Testing

- Prelicensure vaccine trials involve tens of thousands of volunteers
- But there's a statistical limit to trials involving tens of thousands
- Prelicensure testing can rule out a risk of 1 out of a thousand
- It may pick up a risk of 1 out of ten thousand
- It cannot rule out a risk of less than 1 out of ten thousand
- Yet a recommended vaccine may be given to millions a year
- We have systems in place post-licensure to detect safety questions
- We have systems in place to evaluate those safety questions

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Vaccine Adverse Events Reports System or **VAERS**

- FDA and CDC program to receive reports of vaccine problems
- Mandate of federal government
- Vaccine providers, manufacturers must report certain problems
- Patients, parents, others may report
- Registry of adverse events following vaccines
- Not causal but temporal
- Not proof but signal

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Primary Objectives of VAERS

- Detect new, unusual, or rare vaccine adverse events
- Monitor for increases in known adverse events
- Identify potential patient risk factors
- Assess the safety of newly licensed vaccines
- Address possible reporting clusters
- Recognize persistent safe-use problems
- Provide a **national vaccine safety monitoring system**
- Provides signals requiring causal testing for proof

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Vaccine Safety Datalink

- Provides **causal** testing for proof that VAERS cannot
- Program involving CDC and 13 integrated healthcare organizations
  - HealthPartners in Minnesota
  - Marshfield Clinic in Wisconsin
  - Other organizations around the country
- Set up to test safety questions regarding vaccines
- Investigates serious and rare adverse events
- 15% of US population
- Linked vaccines received with patients' records

Types of Studies the Vaccine Safety Datalink Can Do

- Case-control studies
  - Cases of persons with the bad outcome
  - Controls of similar persons who did not suffer the bad outcome
  - Detection of prior receipt of the vaccine in question
- Self-controlled case series
  - The occurrence of the problem during risk time-intervals
    - Before the vaccine would have been given
    - After the vaccine would have been given

One Other System Monitoring Safety Post-Licensure

- FDA has its own active surveillance effort
- Biologics Effectiveness and Safety (**BEST**) System
- 100 million people
- Large-scale claims data, electronic health records, and linked data
- Rapid queries to detect or evaluate adverse events

CISA is Separate from Vaccine Safety Datalink and the FDA

- CISA stands for Clinical Immunization Safety Assessment
- CISA is a national network of vaccine safety experts
  - CDC's own Immunization Safety Office
  - Seven medical research partners, others
- CISA conducts investigations of unusual or new concerns
  - Works with individual medical providers caring for the patient
  - The patient's clinician can request a CISA consultation

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More on VAERS Reporting

- Vaccine Adverse Events Reporting System
- Registry of any adverse events reported
- Manufactures and providers **required** by law to report certain ones
  - Some depend on specific vaccine
  - Most are time-limited after vaccination

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Adverse Events that Vaccine Providers Must Report

- Listed at VAERS web site
- Examples include
  - Severe allergic reaction or anaphylactic reaction following vaccine
  - Shoulder Injury Related to Vaccine Administration
  - Vaccine administration errors
    - Wrong route
    - Wrong dose
    - Wrong individual
- Some adverse events specific to the vaccine

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In Contrast

	Vaccines	Prescription drugs	Over-the-counter	Vitamins and supplements
Prelicensure studies	Yes	Yes	Not necessarily	No
Numbers studied	10,000s	1000	Not necessarily	No
US advisory review	Yes	No	No	No
Postlicensure monitoring	Yes	Yes	Yes	No
VAERS	Yes	No	No	No
Vaccine Safety Datalink	Yes	No	No	No
CISA	Yes	No	No	No

What **Each of Us** Can Do to Assure Vaccine Safety

- Store vaccines appropriately
- Administer vaccines appropriately
- Document vaccines received accurately
- Monitor patient immediately upon giving the vaccine
- Report adverse events that follow vaccine administration
- Investigate patient reports of adverse events thoroughly

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How to Report to VAERS

- Paper form to **mail**
- Paper form to **fax**
- **Online** web-based form to submit

What to **Expect**

- Response in a few days to few weeks
- Phone call or e-mail requesting more details
- Patient or parent may also be contacted

Resources

- CDC Vaccine Safety
  - cdc.gov/vaccinesafety
- Information for Parents and Caregivers
  - cdc.gov/vaccinesafety/caregivers
- Information for Healthcare Providers
  - cdc.gov/vaccinesafety/hcproviders
  - Includes links to VAERS, CISA and more

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Summary

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