How we know vaccines are safe

IMMUNIZE WISCONSIN
MONTHLY WEBINAR SERIES

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Disclosures in the past 2 years

Shareholder:

- CSL (Seqirus)
- GlaxoSmithKline
- Merck
- Moderna
- Novartis
- Pfizer
- Sanofi

Consultant:

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- GlaxoSmithKline
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  - Advisory Committee on Immunization Practices 2016-2020
- Clinician, Family Physician, since 1992
- Medical Educator, since 1996

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Learning Objectives

At the end of this presentation, attendees will be able to:

- Recognize how safety data from clinical trials is reviewed by the United States Food and Drug Administration (FDA) as part of their authorizing the use of vaccines.
- Describe how safety data is incorporated in the development of national vaccination recommendations.
- Explain how the Vaccine Adverse Event Reporting System (VAERS) generates hypotheses and the Vaccine Safety Datalink (VSD) and others investigate hypotheses and assign causality.

Source:

Higher standards of safety for vaccines

Vaccines

Injecting something that is

- sometimes alive into
- healthy people who are
- too young to make medical decisions for themselves

Other medications

Mainly pills by mouth

- simple chemicals taken by
- people who are sick and
- often old enough to decide

How do we know if vaccines are safe?

- Every vaccine goes through many years of study
- 6 Steps in Vaccine Safety
  - National Foundation for Infectious Diseases (NFID)
  - https://www.nfid.org/immunization/vaccine-science-safety/vaccine-safety-steps/
- At every step, scientists have to prove that the vaccine is
  - safe and that it
  - does what it is supposed to do (effective).

6 Steps in Vaccine Safety

- Laboratory Studies in animals
- FDA Review
- Clinical Trials: 3 Phases in humans
- Additional FDA Review
- Vaccine Recommendations
- Ongoing Safety Monitoring

https://www.nfid.org/immunization/vaccine-science-safety/vaccine-safety-steps/

National Foundation for Infectious Diseases

Laboratory studies in animals, FDA review

1 - Test-tube and animal experiments

2 - FDA experts check whether

- scientists did their tests properly
- vaccine looks like it may work
- early warning signs about safety

- If agency approves, start step 3, clinical trials

Clinical trials in humans - Step 3 of 6

- Phase 1
  - Is it safe?
  - Does the body respond?
- Phase 2:
  - How well does it work?
  - More patients, more diverse
- Phase 3:
  - Does it work?
  - Are there rare side effects?

Phase 1 – Clinical trials

- Vaccinate < 100 healthy adult volunteers
- Watch closely for side effects
- Antibody response to different doses

Phase 2 – Clinical trials

- If no major safety problems in phase 1, then
- Vaccinate 100’s of people
  - Different ages, health conditions, and backgrounds
- Which dose gets highest antibody response?
  - Follow up on Phase 1 results
- Any new safety issues in this larger sample?
- If no major safety problems in phase 2, then ...

Phase 3 – Clinical trials

- Vaccinate 1,000's to 10,000's of people
  - Either – new vaccine, comparison vaccine, or placebo
  - Follow people for for months to years
- How many people get the disease that vaccine aims to prevent?
- Which effects are from the vaccine and which are unrelated?
- Any unusual side effects that did not show up in Phase 1 or 2?
- If vaccine prevented disease and no serious safety concerns, then results to FDA for review and authorization for clinical use

When and When Not to Use a Placebo

Every clinical trial compares new vaccine to either a placebo or another vaccine

Use placebo when:

- Disease is new and no other vaccine – early Covid
- No effective vaccine – cytomegalovirus, C. diff
- Old vaccine works poorly in a group – shingles over age 70 years

Unethical to use placebo if effective vaccine already available

- As when replaced whole cell with acellular pertussis in 1990s

FDA review of clinical trial data - Step 4 of 6

- Benefits of protect > risks of side effects?
- If so, FDA authorizes
  - Use in certain groups of people
  - Package insert
  - Description of vaccine, clinical trial results and side effects
  - Manufacturing process, potency of vaccine lots
- FDA may require post-marketing monitoring (phase 4)
  - for uncommon or unexpected side effects.

Vaccine recommendations - Step 5 of 6

After FDA authorizes using a vaccine

Clinical and public health experts decide who should get it and when

https://www.cdc.gov/acip/evidence-based-recommendations/index.html

- How good is the available evidence? – GRADE process
- Evidence-to-Recommendations process
  - How much suffering and premature death does the disease causes?
  - How well does the vaccine prevent infections and illness?
  - How safe is the vaccine?
  - Can it be used fairly across different communities?
  - Are the recommendations
    practical in clinical practice and
    acceptable to the public?

Approved recommendation to insurance

- Official approval of recommendation leads to insurance coverage
- Previously, Advisory Committee on Immunization Practices (ACIP)
  - Approved by Director, Centers for Disease Control and Prevention (CDC)
  - Agreed upon by medical specialty societies
- Now
  - Vaccine Integrity Project (VIP) analyzes clinical trials data
  - Public health committees of medical specialty societies review VIP analysis
  - Specialty societies release recommendations
    - Pediatrics – https://downloads.aap.org/AAP/PDF/AAP-Immunization-Schedule.pdf
    - Family Physicians – https://www.aafp.org/family-physician/patient-care/prevention-wellness/immunizations-vaccines/immunization-schedules.html

Ongoing safety monitoring - Step 6 of 6

Multiple complementary systems with distinct functions

- VAERS – Vaccine Adverse Event Reporting System
  - https://vaers.hhs.gov
- VSD – Vaccine Safety Datalink
  - https://pubmed.ncbi.nlm.nih.gov/21502240
- Additional: BEST, CISA, v-safe

Vaccine Adverse Event Reporting System

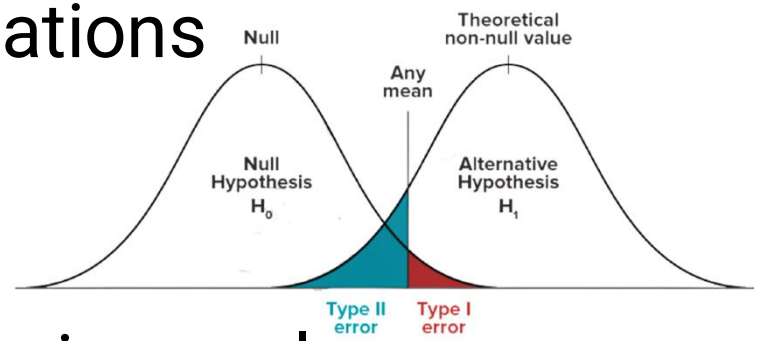
- VAERS = early warning system
- Managed by CDC and FDA
- Passive, spontaneous reporting from healthcare providers, manufacturers, and the public
- Crucial for hypothesis **generation**
- Cannot assess causality

Vaccine Safety Datalink (VSD)

- Hypothesis-**testing** system - Can assess causality
- CDC and 13 integrated health care organizations

  Medical records of 12.5 million people
- Epidemiologic studies

  Case-control and self-controlled case series analyses



- Identified febrile seizures after MMRV vaccine

  https://publications.aap.org/pediatrics/article-lookup/doi/10.1542/peds.2023-065483
- Demonstrated lack of association between vaccines and autism

  https://pubmed.ncbi.nlm.nih.gov/25108215

Additional systems to monitor safety

- FDA's Biologics Effectiveness and Safety (BEST) system
  100 million persons, rapid queries and safety studies
  https://pmc.ncbi.nlm.nih.gov/articles/PMC11260708/
- Clinical Immunization Safety Assessment (CISA) Project
  expert consultation for complex individual cases
  https://pubmed.ncbi.nlm.nih.gov/21502239
- v-safe for COVID-19 vaccines
  smartphone-based active surveillance
  https://pubmed.ncbi.nlm.nih.gov/36697313

Safety surveillance successes

Rare adverse effects resulted in withdrawal of vaccines

- Whole cell pertussis – intractable seizures (Dravet)

  Acellular replacement phased in 1992-1997

  https://pubmed.ncbi.nlm.nih.gov/26203087

- Rotavirus (RotaShield) 1998 – intussusception

  obstruction from bowel folding in on itself
  https://pubmed.ncbi.nlm.nih.gov/10577495

- Covid adenoviral vector, not mRNA, 2021

  clotting of veins in brain -

cerebral venous sinus thrombosis (CVST)

https://jamanetwork.com/journals/jamacardiology/fullarticle/10.1001/jamacardio.2021.3444

Adverse Event Monitoring Systems (AEMS)

Already live in AEMS - March 2026:

- FDA Adverse Event Reporting System - FAERS
  - Drugs, biologics, cosmetics, and color additives
- Vaccine Adverse Event Reporting System - VAERS
- Adverse Event Reporting System
  - Animal drugs and animal foods

https://insider.thefdagroup.com/p/fda-adverse-event-monitoring-system-aems

Migrating to AEMS - May 2026:

- Manufacturer and User Facility Device Experience - MAUDE
  - Medical devices
- Human Foods Complaint System
  - Human foods and dietary supplements
- Tobacco Products Adverse Event Reporting System

AEMS: inexpensive, transparent, corruptible

- Fragmented reporting infrastructure
  - Seven databases
  - 6 million adverse event reports per year
- Expensive, savings expected
  - $37 down to $**13** million annually
- Transparency
  - Publish in real time rather than quarterly
  - Fewer FOIA requests
  - Publicly accessible, searchable dashboard.
  - New AI tools for signal detection, redaction

Potential for increased misuse of VAERS

to claim causality

without VSD, CISA, BEST investigations

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National Foundation for Infectious Diseases

Communicating with patients

- Make simple, clear, consistent recommendations
  - “You are due for vaccines **today** to prevent these diseases”
- Only if objections, then stop & listen to concerns
  - “What is your **main concern**?”
  - Assume patients have their own welfare as the goal
- **Ask for permission** to share
  - 6 Steps in Vaccine Safety (NFID)
  - How vaccines prevent suffering and premature death
- Build trust – **Try again** at future visit

QUESTIONS?

SAVE THE DATE

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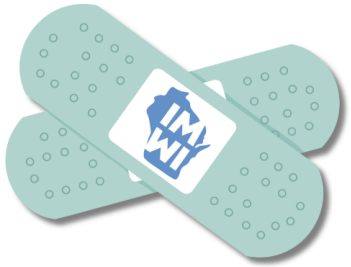
JUNE 11, 2026 | 8:30 AM - 12 PM



STRATEGIES THAT STICK

IMPROVING IMMUNIZATION UPTAKE

A VIRTUAL HALF-DAY CONFERENCE

Immunize Wisconsin is excited to announce our upcoming virtual half-day conference, Strategies That Stick: Improving Immunization Uptake. Mark your calendar and save the date—more details on programming, speakers, and registration will be coming soon.