The Safety of Vaccines

Key points:

- **Vaccines are extensively studied for safety and efficacy prior to licensure**
- **Vaccines have an excellent safety profile. Serious adverse reactions are rare.**
- **The risk of adverse reactions from vaccination is substantially lower than the risk of complications from vaccine-preventable diseases.**
- **Ongoing population surveillance identifies potential rare adverse events (VAERS). Then, well-designed studies are performed to assess causation (VSD).**

The process to ensure that our vaccines are safe

- Vaccines go through a rigorous testing process to ensure their efficacy and safety.
    - **Phase 1 trials:** Include 20-100 patients, primarily evaluate the safety profile of the vaccine
    - **Phase 2 trials:** Include several hundred patients, primarily evaluate the safety profile and immunogenicity of the vaccine
    - **Phase 3 trials:** Include thousands of patients, primarily evaluate the side effects and efficacy of the vaccine
    - **Post-licensure surveillance:** Ongoing population monitoring to identify rare adverse reactions
- **Important definitions:**
    - **Vaccine efficacy** is how well the vaccine works in clinical trials (ex. 80% efficacy means vaccinated group had 80% lower risk of disease compared to the unvaccinated group)
    - **Vaccine effectiveness** is how well the vaccine works in the real world.
    - **Adverse event** is an adverse event that temporally follows vaccination but may or may not be causally related.
    - **Adverse reaction** is an adverse event in which there is substantial evidence to suggest a causal relationship.
- **VAERS (Vaccine Adverse Event Reporting System)**
    - Voluntary reporting system with approx. 30,000 reports/year
    - Has the capacity to identify rare adverse events and safety signals
    - Impacted by reporting bias and lacks a control group
    - Generally, **cannot determine causality**
    - Great for **hypothesis generation**

- **VIS (Vaccine Safety Datalink)**
    - Partnership between CDC and 11 large managed care organizations and 2 sites providing subject matter expertise.[2]
    - **Combines vaccine data with health outcome data**
    - Used for surveillance and research
    - Allows well-designed studies to **test hypotheses to evaluate causality**

The evidence that our vaccines are safe

- In a review of 57 vaccines approved from 1996-2015, **93% of initial FDA approvals were supported by randomized control trials (RCT) data**.[3]
- In a summary of post-marketing surveillance safety modifications[2]
    - **No important safety issues identified**
    - Expanded population restrictions- ex. diminished response in immunocompromised persons (36%)
    - Allergies- 92% related to changes in latex-related packaging
    - Post-vaccination syncope accounted for 21% of all modifications
    - Neurologic complications accounted for 5%- 2 for febrile seizures in infants and 1 for Guillian-Barre Syndrome
    - The single safety withdrawal (RotaShield for intussusception) was identified through VAERS within a year of initial approval.
- In a systematic review of 338 studies on vaccine safety, associations between vaccines approved children, adults and pregnant women and **serious adverse events were rare**.[4]
- A systematic review of adverse events following immunization (AEFI), updating earlier comprehensive safety reviews by the Institute of Medicine in 2012 and the Agency for Healthcare Research and Quality in 2014, examined 46 AEFI and again confirmed vaccines have an excellent safety profile.[5]
    - For 34 AEFI, the evidence did not support as causal relationship with recommended US vaccines.
    - For 12 AEFI, there was an identified causal relationship for at least one vaccine.
        - Transient arthralgia/arthritis: 10-25% of women following rubella immunization
        - Anaphylaxis: 1/100,000-1,000,000 after most commonly administered vaccinations

- Febrile seizures: 3-92/100,000 infants ages 3-5 months (includes all approved vaccines given to infants)
- Gillian-Barre syndrome: 1-3/1,000,000 adults after influenza vaccination

- Statistically, you can never prove the null hypothesis (a vaccine does not cause the AEFI). People casting doubt about vaccine safety often use this argument to cite inconclusive evidence. However, if there is good evidence showing no clear relationship between the vaccine and the AEFI, then it can be concluded the AEFI is not a vaccine reaction.[5]
- For conditions in which evidence is lacking (no safety signal suggesting the need for large scale studies) or insufficient evidence (the limited existing evidence does not show a relationship), it can be concluded that the vaccine has not been shown to cause the AEFI. Existing surveillance systems (ex. VAERS) are very effective at detecting safety signals warranting further evaluation.[5]

References

1. https://www.cdc.gov/vaccine-safety-systems/about/monitoring.html
2. https://www.cdc.gov/vaccine-safety-systems/vsd/index.html
3. Noam Tau, Dafna Yahav, Daniel Shepshelovich. Postmarketing Safety of Vaccines Approved by the U.S. Food and Drug Administration: A Cohort Study. Ann Intern Med.2020;173:445-449. [Epub 28 July 2020].
4. Gidengil C, Goetz MB, Newberry S, Maglione M, Hall O, Larkin J, Motala A, Hempel S. Safety of vaccines used for routine immunization in the United States: An updated systematic review and meta-analysis. Vaccine. 2021 Jun 23;39(28):3696-3716.
5. Dudley MZ, Halsey NA, Omer SB, Orenstein WA, O'Leary ST, Limaye RJ, Salmon DA. The state of vaccine safety science: systematic reviews of the evidence. Lancet Infect Dis. 2020 May;20(5):e80-e89. doi: 10.1016/S1473-3099(20)30130-4.