VACCINE SAFETY

Suzette H. Lazo, MD
Asian Pacific Vaccinology Meeting
Bangkok, Thailand
Nov.30-Dec.3, 2015
Weighing Vaccine’s Benefits versus Risks

- **Vaccine efficacy:** Ability of a vaccine to work as intended to protect from illness.
- **Vaccine-associated risk:** Probability increased adverse event that harm the individuals or population.
Most vaccines have a range of side effects, from mild to serious. Compare the risks of *Haemophilus influenzae* type b (Hib) vaccination with the risks associated with Hib disease.

<table>
<thead>
<tr>
<th>VACCINE SIDE EFFECTS</th>
<th>INFECTION RISKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 5%: fever higher than 101°F (38.3°C)</td>
<td>2% of cases: bone infection</td>
</tr>
<tr>
<td>Up to 25%: redness, warmth, or swelling at the vaccination site</td>
<td>8% of cases: joint infection</td>
</tr>
<tr>
<td></td>
<td>15% of cases: pneumonia</td>
</tr>
<tr>
<td></td>
<td>17% of cases: epiglottitis — infection in the throat that can cause life-threatening airway blockage</td>
</tr>
<tr>
<td></td>
<td>50-65% of cases are Hib meningitis, of which 15-33% lead to permanent neurologic damage (blindness, deafness, or mental retardation) and 2-5% are fatal</td>
</tr>
</tbody>
</table>
ONE OF THE GREATEST PUBLIC HEALTH ACHIEVEMENTS OF ALL TIME!

VACCINES


Now universally mandated
# Revisiting Vaccine’s History

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>Year</th>
<th>Disease</th>
<th>Year</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1885</td>
<td>Cholera</td>
<td>1923</td>
<td>Tuberculosis</td>
<td>1962</td>
<td>Polio (OPV)</td>
</tr>
<tr>
<td>1885</td>
<td>Rabies</td>
<td>1924</td>
<td>Tetanus</td>
<td>1963</td>
<td>Measles</td>
</tr>
<tr>
<td>1891</td>
<td>Anthrax</td>
<td>1926</td>
<td>Pertussis</td>
<td>1967</td>
<td>Mumps</td>
</tr>
<tr>
<td>1896</td>
<td>Typhoid</td>
<td>1927</td>
<td>Tetanus</td>
<td>1969</td>
<td>Meningitis A</td>
</tr>
<tr>
<td>1897</td>
<td>Plague</td>
<td>1935</td>
<td>Yellow fever</td>
<td>1970</td>
<td>Rubella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1943</td>
<td>Typhus</td>
<td>1972</td>
<td>Haemophilus influenza</td>
</tr>
<tr>
<td>1977</td>
<td>Meningitis C (polysaccharide)</td>
<td>1986</td>
<td>Meningitis B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1989</td>
<td>Hepatitis A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1995</td>
<td>Varicella zoster</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1998</td>
<td>Rotavirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1999</td>
<td>Meningitis C (conjugate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2000</td>
<td>Pneumococcal conjugate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Human papilloma virus</td>
</tr>
</tbody>
</table>

WHO Vaccine Safety Basic Manual 2013
<table>
<thead>
<tr>
<th>Year</th>
<th>Incident</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1880s</td>
<td>Pasteur rabies vaccine</td>
<td>→ Seizure, paralysis, coma in 1/230 immunized</td>
</tr>
<tr>
<td>1902</td>
<td>Plague Vaccine: The Mulkowal Incident</td>
<td>→ 19 persons injected with plague vaccine contaminated with tetanus and all died within 7-10 days.</td>
</tr>
<tr>
<td>1942</td>
<td>US military yellow fever vaccine</td>
<td>→ Formulated with human serum; contaminated with infectious hepatitis B virus; 330,000+ infected; 50,000+ with disease; 62 deaths</td>
</tr>
<tr>
<td>1955</td>
<td>Cutter Laboratories incident</td>
<td>→ One of five companies first contracted to produce Salk vaccine; failed to inactivate vaccine preparation (insufficient formalin duration); 120,000 infected; 40,000 mild polio; 200 paralyzed; 10 deaths</td>
</tr>
<tr>
<td>1930</td>
<td>Lubeck Disaster</td>
<td>→ 251 of 452 infants received 3 doses of BCG vaccine by the mouth during the first 10 days of life. Of 251, 72 died of tuberculosis, 135 suffered from clinical tuberculosis but eventually recovered.</td>
</tr>
</tbody>
</table>
VACCINE ADVERSE EVENTS DUE TO RARE BIOLOGICAL EVENTS

- Acute encephalopathy after whole-cell pertussis vaccine
- Guillain–Barré syndrome (GBS) after swine flu vaccine
- Acute arthropathy following rubella vaccine
- Paralytic polio following live, attenuated oral polio vaccine (OPV)
- Thrombocytopenia following measles virus-containing vaccine
- Anaphylaxis following receipt of vaccines containing egg proteins or gelatin
HOW VACCINES DIFFER FROM OTHER DRUGS

- Complex protein molecules; more stringent regulations
  - More complicated protein molecular structures
  - Immunogenic
  - Production more complicated; unstable-distribution and storage requires controls
  - Subject to lot release program

- Target high population (e.g., birth cohorts); universal global mandate

- Schedule protects before age of greatest risk; period of life coincides with emergence of underlying disease (e.g., neurodevelopmental disorders)

- AEFI; causality assessment complicated by inability to readily “dechallenge” and reluctance to “rechallenge”
VACCINE COMPONENTS THAT CAN CAUSE REACTIONS:

• Antigen (active component of the vaccine)
• Adjuvant – Aluminum salts, AS03, AS)4, MF59)
• Preservative – thimerosal
• Stabilizer – gelatin
• Antibiotics – neomycin
• Others – pH, osmolarity
Vaccines: Success into weakness

Effect of Vaccination on Disease Incidence

Potential stages in the evolution of an immunisation programme.

NEED FOR VACCINE SAFETY HAS BECOME MORE URGENT

General public has low tolerance to adverse events as vaccines are usually given to healthy persons.

Expectation to safety standard is higher with vaccines compared to medicines for sick people.

National regulatory authorities (NRAs) ensure with rigor the quality, safety, & effectiveness of vaccines and pharmaceutical products.

Once introduced, vaccines are thoroughly and continuously reviewed.

NRAs monitor and investigate AEFIs to ensure safety for population.

Before being introduced, vaccines are assessed in clinical trials.

WHO 2013

Low tolerance requires safe vaccination
VACCINE SAFETY
FROM INCEPTION TO PRODUCTION

Prelicensure Evaluations of Vaccine Safety

**Phase 1**
- Involves, typically, 20-80 participants
- Is used to evaluate safety and the most appropriate dose and dosage

**Phase 2**
- Further evaluates safety and efficacy and continues to determine vaccine dose in larger numbers of subjects (usually 100-300 participants)

**Phase 3**
- Involves much larger numbers of subjects (1000 to 3000) and is used to confirm efficacy, collect additional safety information and, if applicable compare with existing vaccines.
Post-licensure Surveillance is necessary!

- Pre-Licensure studies of new vaccines not large enough to detect all serious and rare AEs.
- Identify rare reactions/ monitor increases in known reactions
- Identify risk factors for AEs/higher risk groups
- Identify signals
- Identify vaccine lots with unusual rates or types of AEs
- Public confidence in vaccines
Adverse Events Following Immunization (AEFI) Surveillance

- Detect, correct, and prevent programme errors
- Identify problems with vaccine lots or brand
- Maintain confidence by properly responding to parent/community concerns while increasing awareness (public and professional) about vaccine risks
- Estimate rates of occurrence on AEFI in the local population, compared with trial and international data; identify increases in known reactions
Global Vaccine Safety Monitoring

Global capacity building and harmonized tools:
- Brighton Collaboration
- CIOMS/WHO working group
- Training providers

Global advice and response:
- GACVS
- Other global or regional advisory bodies

National AEFI surveillance, investigation and response:
- National regulatory authority
- National immunization programme
- AEFI review committee
- Other support groups

Product monitoring:
- Vaccine manufacturers
- Licensing authorities in country of manufacture
- Procurement agencies

Global signal, evaluation and detection:
- WHO PIDM
- Global Vaccine Safety DataNet
- Other partners
INSTITUTE OF MEDICINE
(NATIONAL ACADEMIES PRESS)

- MMR and Autism (2001)
- Thimerosal and Neurodevelopmental Disorders (2001)
- Multiple Immunizations and Immune Dysfunction (2002)
- HepB Vaccine and Demyelinating Neurological Disorders (2002)
- SV40 Contamination of Polio Vaccine and Cancer (2002)
- Influenza vaccines and Neurological Complications (2003)
Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

AUTHORS: Margaret A. Maglione, MPP, Lopamudra Das, MPH, Laura Raen, MPH, Alexandria Smith, MPH, Ramya Chari, PhD, Sydne Newberry, PhD, Roberta Shanman, MLS, Tanja Perry, BHM, Matthew Bidwell Goetz, MD, and Courtney Gidengil, MD, MPH

RAND Corporation, Santa Monica, California; VA Greater Los Angeles Healthcare System and David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, and Boston Children’s Hospital, Boston, Massachusetts

Abstract

BACKGROUND: Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. This study systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States.

RESULTS: Of 20,478 titles identified, 67 were included. Strength of evidence was high for measles/mumps/rubella (MMR) vaccine and febrile seizures; the varicella vaccine was associated with complications in immunodeficient individuals. There is strong evidence that MMR vaccine is not associated with autism. There is moderate evidence that rotavirus vaccines are associated with intussusception. Limitations of the study include that the majority of studies did not investigate or identify risk factors for AEs; and the severity of AEs was inconsistently reported.

CONCLUSIONS: We found evidence that some vaccines are associated with serious AEs; however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide. Pediatrics 2014;134:1-13
THIMEROSAL AND THE DANISH STUDY

• Denmark has extensive medical records of its citizens
• Abandoned thimerosal in childhood vaccines in 1992
• Evaluated the incidence of autisms in children immunized with thimerosal-free and thimerosal-containing vaccines
• Results
  • 956 autistic children
  • 3.5:1 male: female ratio
  • From 1970 to 1990, no increased incidence of autisms was observed
• After removal of thimerosal, the incidence of autisms began to increase

TABLE 1  VSD Strategic Priorities
Evaluate the safety of newly licensed vaccines
Evaluate the safety of new vaccine recommendations for existing vaccines
Evaluate clinical disorders after immunizations
Assess vaccine safety in special populations at high risk
Develop and evaluate methodologies for vaccine-safety assessment
Clinical Immunization Safety Assessment (CISA) Project

- Improve understanding of vaccine safety issues at individual level
- Review individual cases
- Develop strategies to assess individuals
- Conduct studies to identify risk factors
THE PROVIDER’S ROLE

Immunization providers can help ensure the safety and efficacy of vaccines through:

• Study of products (labels & publications) and observing contraindications & precautions
• Implementing proper timing and spacing of vaccine doses
• Management of vaccine side effects
• Reporting of suspected side effects
• Communicating vaccine benefits versus risk considerations
• Adherence to proper storage, dispensing and administration practices.
NEED FOR IMPROVED COMMUNICATION

Communicate only reliable information

Simplify Key Messages

Risk Perception

The public sees risk in terms of:
- Voluntariness of exposure,
- Familiarity of risk,
- Control over risk,
- Catastrophic potential,
- Fatal outcomes,
- Unequal balance between risk & benefit,
- Unequal distribution of risk.

Experts see risk in terms of:
- Morbidity and mortality levels
RESULTS: The mean number of vaccine-safety articles per state was 26. Six (not mutually exclusive) topics were identified: vaccine-safety concerns (46%); vaccine policy (44%); vaccines are safe (20%); immunizations are required (10%); immunizations are not required (8%); and state/school exemption (8%). Three spikes in the number of newspaper articles about vaccine-safety issues were observed: in 1999 regarding rotavirus vaccine and in 2002 and 2003 regarding smallpox vaccine. Excluding articles that referred to rotavirus and smallpox vaccines, 37% of the articles had a negative take-home message.

CONCLUSION: Ongoing monitoring of news on vaccine safety may help the content and framing of vaccine-safety messages. Pediatrics 2011; 127:S100–S106
Application of pharmacogenomics to vaccines

Gregory A Poland\textsuperscript{1,2,3,†}, Inna G Ovyannikova\textsuperscript{1,2}, and Robert M Jacobson\textsuperscript{1,3,4}

\textsuperscript{1}Mayo Vaccine Research Group, MN, USA

\textsuperscript{2}Program in Immunovirology & Biodefense, Mayo Clinic, College of Medicine, 611C, Guggenheim Building, 200 First Street, SW Rochester, MN, 55905, USA

\textsuperscript{3}Department of Medicine, Mayo Clinic, MN, USA

\textsuperscript{4}Department of Pediatric & Adolescent Medicine, Mayo Clinic, MN, USA

Abstract

The field of pharmacogenomics and pharmacogenetics provides a promising science base for vaccine research and development. A broad range of phenotype/genotype data combined with high-throughput genetic sequencing and bioinformatics are increasingly being integrated into this emerging field of vaccinomics. This paper discusses the hypothesis of the ‘immune response gene network’ and genetic (and bioinformatic) strategies to study associations between immune response gene polymorphisms and variations in humoral and cellular immune responses to prophylactic viral vaccines, such as measles–mumps–rubella, influenza, HIV, hepatitis B and smallpox. Immunogenetic studies reveal promising new vaccine targets by providing a better understanding of the mechanisms by which gene polymorphisms may influence innate and adaptive immune responses to vaccines, including vaccine failure and vaccine-associated adverse events. Additional benefits from vaccinomic studies include the development of personalized vaccines, the development of novel vaccines and the development of novel vaccine adjuvants.
Towards designing safer & more effective vaccines