REPORT TO THE BOARDS OF HEALTH

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Monitoring for Adverse Events after Vaccine

Worldwide, vaccines prevent 2 to 3 million deaths every year and continue to prevent hundreds of thousands of cases of illness, complications, and disability in the United State each year (see table, right). Vaccinations are one of the most successful public health developments to extend and improve our lifespan. A vaccine is a medical product and just like any other medication, there can be side effects. Most side effects from vaccines are mild, and resolve quickly and completely. There are chances for rare but severe events after vaccination, such as severe allergic reaction (anaphylaxis). Other adverse events can follow an immunization, but they are not necessarily caused by the vaccine. As more people are vaccinated and the disease becomes less common, there is less tolerance to any potential side effects.

Impact of Vaccines in the 20th & 21st Centuries

Comparison of 20th Century Annual Morbidity & Current Morbidity: Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity*	2017 Reported Cases†	% Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Pertussis	200,752	18,975	91%
Tetanus	580	33	94%
Polio (paralytic)	16,316	0	100%
Measles	530,217	120	>99%
Mumps	162,344	6,109	96%
Rubella	47,745	7	>99%
CRS	152	5	97%
Haemophilus influenzae	20,000 (est.)	33§	>99%

* *JAMA*. 2007;298(18):2155-2163
† CDC. *National Notifiable Diseases Surveillance System, 2017 Annual Tables of Infectious Disease Data*. Atlanta, GA. CDC Division of Health Informatics and Surveillance, 2018. Available at: www.cdc.gov/nndss/infectious-tables.html. Accessed on December 3, 2018. NNDSS finalized annual data as of November 28, 2018.
§ *Haemophilus influenzae* type b (Hib) <5 years of age. An additional 10 cases of Hib are estimated to have occurred among the 203 notifications of Hi (<5 years of age) with unknown serotype.

Comparison of Pre-Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

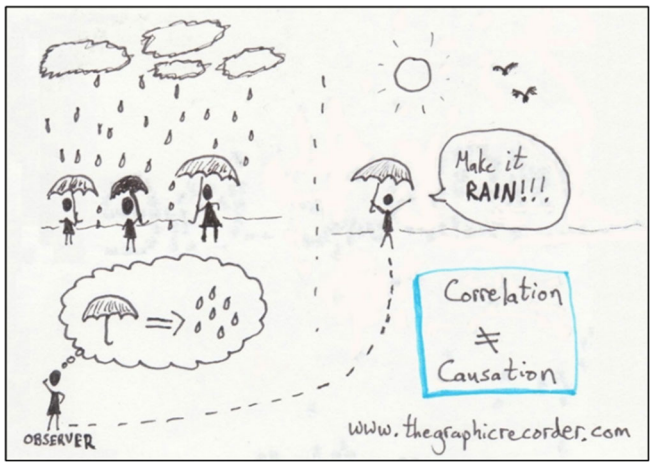
Disease	Pre-Vaccine Era Annual Estimate	2016 Estimate (unless otherwise specified)	% Decrease
Hepatitis A	117,333*	4,000†	97%
Hepatitis B (acute)	66,232*	20,900†	68%
Pneumococcus (invasive)			
All ages	63,067*	30,400¶	52%
<5 years of age	16,069*	1,700¶	89%
Rotavirus (hospitalizations <3 years of age)	62,500‡	30,625§	51%
Varicella	4,085,120*	102,128††	98%

* *JAMA*. 2007;298(18):2155-2163
† CDC. Viral Hepatitis Surveillance – United States, 2016
¶ CDC. Unpublished. Active Bacterial Core surveillance. 2016
‡ CDC. *MMWR*. February 6, 2009 / 58(RR02): 1-25
§ New Vaccine Surveillance Network 2017 data (unpublished); U.S. rotavirus disease now has biennial pattern
†† CDC. Varicella Program 2017 data (unpublished)

An adverse event following vaccination is any unexpected medical situation that happens after a vaccine is received but is not necessarily caused by the vaccine. Adverse events following vaccination are grouped into five categories:

1. **Vaccine reaction.** In a vaccine reaction, the person getting the vaccine had a response to something in the vaccine. It could be due to how our bodies naturally respond to the vaccine. It usually happens within minutes to hours of getting the vaccine. They can be minor reactions, such as pain, swelling or redness at the site of injection, fever, muscle pain, headache, or loss of appetite. These events usually pass quickly and pose little danger. There can also be more severe reactions, like allergic reaction or seizure, which are rare, and typically do not result in any long-term problems. However, severe reactions like anaphylaxis can very rarely be fatal, especially if proper treatment is not available.
2. **Vaccine quality/defect reaction.** These types of reactions are due to a defect with the vaccine product itself. There could be contamination in the vaccine that causes illness or infection.
3. **Immunization error.** One of most common causes for reactions, this is due to errors in preparation, storage, handling, or administration of a vaccine. These errors can lead to reactions, infections, or injuries at the injection site, ineffective vaccine, missing a contraindication which leads to a severe allergic reaction, etc.

4. **Immunization anxiety reaction.** Another common cause for reaction, this is not related to the vaccine, but the fear and anticipation of getting an injection. This can include fainting, hyperventilation, vomiting, convulsions, and panic attacks. Injuries, sometimes serious, can occur due to falls from fainting. Fainting may not happen right away and could happen to someone later while driving causing accidents. For this reason, it is important to wait for 15 minutes after vaccinations.



5. **Coincidental event.** When there is a medical problem that happens after a vaccine is given but was not caused by the vaccine, it is a coincidental event. This can include many things, like coincidental death, onset of developmental disorders, autoimmune disorders, etc. It is important to remember that correlation is not the same as causation, or just because you did one thing and another thing happened, it does not mean the one thing caused another thing to happen. It is important to compare how often the medical problem occurs in those getting vaccinated to how often it occurs in the same type of people that did not getting vaccinated.

To better understand the concerns about adverse events after vaccination and the systems that we have to watch for possible problems, it is important to look back at some of the side effects, errors, and concerns that have and have not been due to vaccinations over the past one and a half centuries.

Historic Vaccine Safety Issues

- In the late 1800s, the first rabies vaccines were made using animal brains and spinal cords. The vaccine did prevent certain death from rabies, however it caused serious side effects in up to 1 in 230 persons such as seizures, paralysis, and even coma.
- In the 1940s, a yellow fever vaccine was used in the U.S. military which used human serum (a blood product from people) as part of the vaccine. Unfortunately, due to the lack of knowledge and screening at the time, some of the serum came from people infected with hepatitis B. As a result, 330,000 soldiers were infected with hepatitis B, 50,000 developed severe liver disease, and 62 died.
- In the 1950s, several companies were making the life-saving polio vaccine. This vaccine used a polio virus that had been inactivated by formaldahyde. One company, Cuttler Laboratories, did not completely inactivate the virus and their vaccine caused mild polio in 40,000 children, leading to permanent paralysis in 200 and death in 10. It is refered to as “the Cuttler incident” and is one of the worse biologic incidents in U.S. history.
- In 1976, a swine flu vaccine was developed and rapidly deployed after cases of swine flu were discovered at a U.S. army base in New Jersey. It was noted there was a small increased risk of a serious neurological disorder called Guillain-Barré Syndrome (GBS) following this vaccination, or about one additional case of GBS for every 100,000 swine flu vaccines given. The vaccination was stopped. A review in 2009 showed that no other flu vaccine has been a definite cause of GBS. In fact, infection with influenza was found to put people at a much higher risk of causing GBS.
- In 1998, the first vaccine for rotavirus, RotaShield, was approved. It was noticed that some infants developed intussusception, a rare type of bowel obstruction, after being vaccinated. The Centers for Disease Control and

Prevention (CDC) recommended that the vaccine be suspended and started an emergency investigation. They felt the vaccine was the cause of the intussusception and the vaccine was withdrawn from the market.

False Vaccine Safety Concerns

- In the 1950s, two British doctors found 36 children that had developed neurologic issues after getting a pertussis (whooping cough) vaccination. Several similar reports appeared after this. England and the United States did large studies which confirmed the safety of the pertussis immunization. Pertussis vaccines at that time were made with the whole cell bacteria that was inactivated and was known to cause more reactions like fever, redness, fussiness, crying, and even febrile seizure (a seizure due to a high fever.) Unfortunately, there was continued worldwide concern and controversy over the pertussis vaccine in the 1970s and 1980s. There were television documentaries, and a book published over safety concerns. There were several lawsuits against pertussis vaccine manufacturers. Companies started to pull out of vaccine manufacturing due to the expense. Some countries stopped using the vaccine and many countries saw a decrease in vaccination rates. Whooping cough rates and deaths spiked dramatically from the late 1970s to 1980s. Significant efforts began to find a more acceptable pertussis vaccination, DTaP, which uses an acellular pertussis vaccination. It produces much fewer side effects, however, it also appears to be less effective than DTP.
- Deaths occuring in the time period after any vaccination are often blamed on the vaccine. We see that occurring now with the COVID-19 vaccines. Evidence has never been found to suggest any cause-effect relationship between any vaccination and death except for the very rare exception of anaphylaxis. Otherwise, these deaths are coincidental.
- The most controversial and argued issue in the last several decades has been that vaccines, specifically MMR, cause autism. Autism is a chronic developmental disorder that is currently felt to have genetic causes. Imaging, like MRI and ultrasound, shows changes in an autistic baby's brain about halfway through gestation, or before birth. Since symptoms do not typically appear until around age 1 to 2 years old, which is near the time MMR is given, many parents and doctors have blamed the vaccine. This fear was increase in 1998 when a study was published by Andrew Wakefield, a British gastroenterologist, along with 12 other co-authors. The study evaluated 12 children with colitis and developmental disorders, reporting there was a link between these conditions and receiving the MMR vaccine. As a result, MMR vaccination rates dropped in the U.S. and Britain. Many scientists tried to reproduce Wakefield's study or find supporting evidence and could not. His original research was evaluated and the parents of the 12 children interviewed. It was found much of his data was falsified and discovered he was paid by attorneys that wanted to sue vaccine manufacturers. In 2010, the paper was officially retracted from the Lancet, and Wakefield was banned from practicing medicine in Britain.
- It has been argued that a preservative previously used widely in vaccines, called thimerosal, increased risks of autism. Of note, thimerosal has never been used in MMR. Numerous large studies have found no connection between thimerosal and autism. In fact, Denmark saw an increase in autism several years after they stopped use of thimerosal in 1991. However, as a precaution, thimerosal has not been used in childhood vaccines since 2002. It is only used in some multi-dose vials of flu vaccine.

  The Autism Science Foundation, https://autismsciencefoundation.org/, is focused on discovering the causes of autism, the importance of early diagnosis and early intervention, and that vaccines save lives. The foundation supports that vaccines do not cause autism.

There have been several very expensive court cases against drug companies. Some were due to legitimate claims, such as polio occurring after the use of the live oral polio vaccine. This was a very rare and known complication, yet parents were not always advised of that possibility (i.e., not being given informed consent). Other lawsuits were due to events never proven to be caused by the vaccine, such as a $1.1 million verdict for transverse myelitis after

DTP vaccine in *Toner v Lederle Laboratories* in 1986. As discussed above, there was a lot of concern regarding the DTP vaccine at this time and combined with a very litigious atmosphere in the 1980s, and large rewards being granted from juries, many drug companies stopped manufacturing vaccines.

In order to protect the supply of vaccines, Congress passed the National Childhood Vaccine Injury Act (NCVIA) in October 1986, which included requirements to provide informed consent before vaccination, including a Vaccine Information Statement (VIS) with certain vaccines, and required reporting of adverse events (see VAERS, below). It also placed a $0.75 tax on each vaccine dose, collected from the manufacturer, to fund the National Vaccine Injury Compensation Program (NVICP), which is used to fairly compensate those that suffer a recognized adverse event from certain vaccines that have been properly manufactured. Covered vaccines and recognized adverse events can be found here https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf.

Before vaccines are licensed, they go through several phases of study, just like other drugs. The effectiveness and the safety of a vaccine are studied closely in these trials. After vaccines are licensed, there are many ways safety is monitored in several ways. The Vaccine Adverse Events Reporting System (VAERS), which was created as part of the National Childhood Vaccine Injury Act, is a joint project of CDC and FDA implemented in 1990. It is a centralized area for reporting any clinically significant adverse event after vaccination, including those that are mandated by healthcare providers. Anyone can report to VAERS, not just healthcare providers. VAERS data is entered into a database without any personal identifiers by a contractor outside of the CDC and FDA. More information is collected if needed. All this data is available to the public (at www.vaers.hhs.gov and at www.wonder.cdc.gov/vaers.html). Several other countries have similar monitoring systems. The World Health Organization (WHO) compiles data on adverse vaccine events along with other drugs at their Collaborating Center for International Drug Monitoring in Uppsala, Sweden.

VAERS is meant to be a signaling agent, not a scientific database. If the system detects an unusual pattern, more evaluation is needed. An example occurred in 2005 when a new meningitis vaccine (Menactra) was licensed. There was an increased number of Guillain-Barré Syndrome (GBS) cases noted in VAERS shortly after this. There were two large studies that followed, one reviewed data from five health plans with more than 1.4 million vaccinations given and found there was no increased risk of GBS compared to those that did not get vaccinated. A more recent example is the Johnson and Johnson COVID-19 vaccine. The VAERS system was able to detect six reports of rare blood clots in the brain associated with low platelets shortly following vaccination. This is following 7.5 million doses given in the United States. This unusual event signalled concern, and the CDC and FDA have put use of the vaccine on pause while more information can be gathered and evaluated.

Another safety monitoring system is the Vaccine Safety Datalink (VSD) project started in 1990. In this project, the CDC collaborates with 9 large healthcare organizations. Whenever there is a new vaccine or a change in vaccine recommendations, the electronic health data from these healthcare organizations is used to follow information on vaccination as well as any diagnosed medical illnesses to monitor for adverse events and conduct research. More information availabe here https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html#access.

The Clinical Immunization Safety Assessment (CISA) Project was established by the CDC in 2001 and is a network of vaccine safety experts from the CDC, research centers, and subject-matter experts. They partner in studies to identify risk factors for adverse events to vaccinations as well as ways to prevent them. They also serve as subject-matter experts as needed when evaluating adverse events. More information available at https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html.

When a mass vaccination campaign must be held, as in a pandemic such as H1N1 and COVID-19, additional monitoring is needed to be able to detect any potential problems early. Like the VSD, databases from several large

health plans, the Department of Defense, Medicare, and the Veterans Administration are analyzed on a rapid and ongoing basis during these times.

The CDC initiated V-safe, a smartphone-based tool, with the onset of COVID-19 vaccination. This tool uses text messages with web surveys to screen for side effects after vaccination. The screening continues for several weeks past the last dose of vaccination. More information available at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html.

All of this monitoring is to help determine if an adverse event following a vaccine was caused by that vaccine. This determination relies on evaluating all the evidence for things like strength of association, consistency of these findings, relationship to vaccination timing, and whether the adverse event makes physiologic and biologic sense. The Institute of Medicine, Agency for Healthcare Research and Quality, and internationally, the World Health Organization, have identified adverse reactions that have strong evidence of being caused by vaccination and are listed in the table below, along with the rate they are estimated to occur.

TABLE 82.3 Vaccines and Adverse Events for Which Evidence Favors a Causal Association

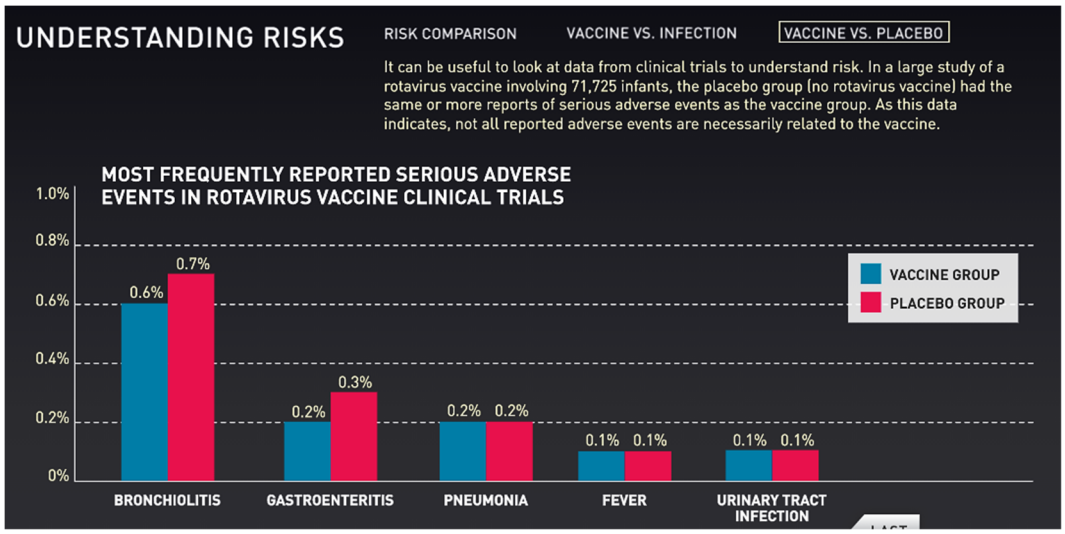
Vaccine(s)	Adverse Event	Source	Rate Per Million Doses
Tetanus toxoid, pertussis, measles, mumps, rubella, inactivated polio vaccine, hepatitis B, varicella, influenza, meningitis, human papillomavirus	Anaphylaxis	VIT, IOM2012	1–2[a]
Pertussis (whole cell)	Encephalopathy/encephalitis	VIT	<1[b]
Measles-mumps-rubella (MMR)	Encephalopathy/measles inclusion body encephalitis	VIT, IOM2012	Case reports only
MMR	Febrile seizures	IOM 2012	333[b]
MMR	Transient arthralgia, women & children	IOM 2012	~5% (postpartum women) <1% (children)
Measles	Thrombocytopenic purpura	VIT	33[b]
Rubella	Chronic arthritis	VIT	Unknown[c]
Varicella	Vaccine strain dissemination	IOM 2012	Case reports
Any vaccine	Injection-related syncope, deltoid bursitis	IOM 2012	Case reports

[a]Data from McNeil MM, Weintraub E, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868–178.

[b]Data from World Health Organization (WHO), Department of Vaccines and Biologicals. Supplementary information on vaccine safety, Part 2: Background rates of adverse events following immunization. December 2000. WHO/V&B/00.36. Available at: http://apps.who.int/iris/bitstream/10665/66675/1/WHO_V-B_00.36_eng.pdf

[c]IOM 2012 review determined evidence to be inadequate.

IOM, Institute of Medicine; U.S.; VIT, Vaccine Injury Table, U.S.



The History of Vaccines, An Educational Resource by the College of Physicians of Philadelphia https://www.historyofvaccines.org/

Healthy Living Recommendations

1. Given the ease of global travel and declining vaccination rates, the risk from vaccine-preventable diseases is higher than ever. Vaccines have an extremely small risk of severe side effects or serious risks and the benefits outweigh the risks.
2. The national and global vaccine safety monitoring systems have proven themselves to be very effective at detecting potential adverse events following vaccination.

Sources

- Global Immunization: Worldwide Disease Incidence, Children's Hospital of Philadelphia (CHOP) https://www.chop.edu/centers-programs/vaccine-education-center/global-immunization/diseases-and-vaccines-world-view
- World Health Organization (WHO) Vaccine Safety Basics: Module 3: Adverse Events Following Immunization, https://vaccine-safety-training.org/classification-of-aefis.html
- Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds.
- Plotkin, Stanley A, Walter A. Orenstein, Paul A. Offit, and Kathryn M. Edwards. Plotkin's Vaccines, 2018. Print.
- Morse, J. (2016). Comparison of the Efficacy and Adverse Events of Whole-Cell Pertussis and Acellular Pertussis Vaccine.
- The History of Vaccines, An Educational Resource by the College of Physicians of Philadelphia https://www.historyofvaccines.org/