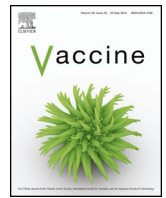




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## 1 Q1 Review

## 2 Deaths following vaccination: What does the evidence show?☆

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### A B S T R A C T

Vaccines are rigorously tested and monitored and are among the safest medical products we use. Millions of vaccinations are given to children and adults in the United States each year. Serious adverse reactions are rare. However, because of the high volume of use, coincidental adverse events including deaths, that are temporally associated with vaccination, do occur. When death occurs shortly following vaccination, loved ones and others might naturally question whether it was related to vaccination. A large body of evidence supports the safety of vaccines, and multiple studies and scientific reviews have found no association between vaccination and deaths except in rare cases. During the US multi-state measles outbreak of 2014–2015, unsubstantiated claims of deaths caused by measles, mumps, and rubella (MMR) vaccine began circulating on the Internet, prompting responses by public health officials to address common misinterpretations and misuses of vaccine safety surveillance data, particularly around spontaneous reports submitted to the US Vaccine Adverse Event Reporting System (VAERS). We summarize epidemiologic data on deaths following vaccination, including examples where reasonable scientific evidence exists to support that vaccination caused or contributed to deaths. Rare cases where a known or plausible theoretical risk of death following vaccination exists include anaphylaxis, vaccine-strain systemic infection after administration of live vaccines to severely immunocompromised persons, intussusception after rotavirus vaccine, Guillain-Barré syndrome after inactivated influenza vaccine, fall-related injuries associated with syncope after vaccination, yellow fever vaccine-associated viscerotropic disease or associated neurologic disease, serious complications from smallpox vaccine including eczema vaccinatum, progressive vaccinia, postvaccinal encephalitis, myocarditis, and dilated cardiomyopathy, and vaccine-associated paralytic poliomyelitis from oral poliovirus vaccine. However, making general assumptions and drawing conclusions about vaccinations causing deaths based on spontaneous reports to VAERS – some of which might be anecdotal or second-hand – or case reports in the media, is not a scientifically valid practice.

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## 21 1. Background

22 Q4 Modern vaccines are among the greatest public health achievements in history, preventing thousands of illnesses and deaths each year in the United States alone [1]. However, as illness, disability

25 and death from vaccine-preventable diseases have decreased, concerns over vaccine safety have increased [2]. Despite the reality that a person is far more likely to be seriously or fatally injured by a disease prevented by vaccines than by a vaccine itself, there appears to be a trend toward increased refusal or delay of recommended vaccinations due to perceived safety concerns [3].

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During the US multi-state measles outbreak of 2014–2015, most infected persons were not vaccinated against measles or had unknown vaccination status [4]. Early on, unsubstantiated claims of deaths caused by the measles, mumps, and rubella (MMR) vaccine began circulating on the Internet [5–7]. The original claim was based on data from the US Vaccine Adverse Event Reporting System (VAERS). It is important to realize, however, that VAERS is a voluntary reporting system which accepts any submitted report of an adverse event without judging its clinical significance or whether it was caused by a vaccination [8]. VAERS is a signal detection and hypothesis generating passive surveillance system and therefore

*Abbreviations:* ACIPA, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; IOM, Institute of Medicine; MMR, measles, mumps, & rubella combination vaccine; OPV, oral poliovirus vaccine; SIDS, sudden infant death syndrome; VAERS, Vaccine Adverse Event Reporting System; VAPP, vaccine-associated paralytic polio.

☆ Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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any broad claim of cause and effect with respect to deaths following vaccination based on VAERS reports should not be interpreted as proof of causality.

We summarize historical information and published epidemiologic data on deaths following vaccination, including events where reasonable scientific evidence exists to conclude that vaccination caused or contributed to deaths. There are instances where medical errors or other human factors, not the vaccine as it was meant to be used, have caused deaths following vaccination [9,10]. However, our summary is restricted to deaths possibly related to the vaccine itself.

## 2. Historical events

In the era of modern medicine, some of the first concerns about vaccines causing death date to isolated, but high profile past vaccine safety incidents. The “Cutter Incident” in 1955 involved a flaw in the Salk polio vaccine manufacturing process at Cutter Laboratories that led to production of substantial amounts of what was thought to be inactivated vaccine that contained live poliovirus. The result has been called “. . .one of the worst pharmaceutical disasters in US history” [11], with 40,000 cases of polio resulting in 51 cases of permanent paralysis and five deaths among vaccinated individuals, and 113 cases of paralysis and five deaths among contacts of vaccinated individuals [11,12]. As a result of the Cutter Incident, the US government implemented much more vigilant monitoring and regulation of the vaccine industry [13]. The Food and Drug Administration (FDA) now requires extensive testing to evaluate the safety and efficacy of vaccines prior to licensure. After licensure, FDA requires ongoing lot-release testing and manufacturing facility inspections. Additionally, manufacturers are required to conduct post-licensure safety monitoring for their products and report to the FDA [14,15].

In 1976, concerns in the United States about a possible influenza pandemic involving a virus similar to the deadly 1918 pandemic strain resulted in a large-scale vaccination program for the entire country. Approximately 45 million people were vaccinated in 10 weeks with what became known as the “swine flu vaccine” [16]. The US government abruptly stopped the vaccination program when no swine flu cases were detected outside the military base where the disease originated and when an unexpectedly high number of cases of Guillain–Barré syndrome were reported in vaccinated individuals. The vaccine was estimated to have caused approximately one Guillain–Barré syndrome case per 100,000 persons vaccinated [17], resulting in 53 deaths [18]. As a result of the association between the 1976 swine flu vaccine and Guillain–Barré syndrome, this condition is closely monitored every influenza season as part of the influenza vaccine safety monitoring in the United States.

## 3. Current epidemiologic data on death associated with vaccination

Multiple large reviews and studies have been conducted to evaluate the association between vaccination and death. The results have consistently been reassuring. The Institute of Medicine (IOM) reviewed deaths reported to VAERS after childhood vaccines in the early 1990s [19]. Some of the reports did not have enough information to make a determination about causality, but among reports with adequate follow-up, the IOM concluded that the vast majority of reported deaths were coincidental and not causally related to vaccination. There was one death due to a vaccine strain viral infection: a 3-month-old infant died from myocarditis after oral polio vaccine (which is no longer licensed for use in the United States) and DTP vaccine; vaccine strain poliovirus was isolated from the child’s myocardium. In another review of 1266 deaths reported to

VAERS from 1990 to 1997, nearly half of the deaths were due to sudden infant death syndrome (SIDS) with a peak in 1992–1993 and a decline after the “Back to Sleep” campaign was implemented [20]. The study also found that death reports to VAERS from causes other than SIDS also declined from 1993 to 1996 as the population and the number of vaccines administered increased, which was reassuring. In addition to SIDS, there were multiple causes of death which were not vaccine related, including infectious, congenital, neoplastic, cardiac, and cases with unknown causes due to incomplete information. This review also found that among the death reports, a higher percent of the infants had low birth weight than in the general US population (16.8% vs. 7.2%); lower birth weight infants are known to have higher mortality rates during the first 2 years of life [20]. Multiple other published reviews of VAERS data for specific vaccines and vaccine types have found no concerning patterns that would suggest a causal relationship between vaccination and deaths [21–26].

In 2003, the IOM examined the relationship between vaccinations and SIDS. The IOM rejected a causal association between the whole cell pertussis-containing vaccine (which is no longer in use in the United States) and SIDS and between exposure to multiple vaccines and SIDS. The IOM concluded that inadequate evidence existed to accept or reject a causal relationship between several other vaccines and SIDS. Additionally, the IOM did “. . . not recommend a policy review of the recommended childhood vaccination schedule by any of the national or federal vaccine advisory bodies on the basis of concerns about sudden unexpected death in infancy” [27].

A study published in 2013 using electronic health record databases reviewed health information on over 13 million vaccinated persons and compared causes of death in the vaccinated study population to the general US population. The death rate 1 or 2 months following vaccination was lower than that in the general US population, and the causes of death were similar [28]. This study provides convincing evidence that vaccinations are not associated with an increased risk of death at the population level.

## 4. Evidence in favor of causal associations between vaccination and death

Although the evidence supports the safety of vaccines, there are rare instances where causal relationships between vaccination and death have been established or a plausible theoretical risk exists.

### 4.1. Anaphylaxis following vaccination

Many vaccines have been determined to rarely cause anaphylaxis. The risk of anaphylaxis is less than two cases per million doses of vaccines administered to children and adolescents [29]. While anaphylaxis is serious and can be fatal, death and other complications can be prevented with rapid treatment using effective medications including epinephrine, corticosteroids and beta-agonists. A 10-year review of claims to the US National Vaccine Injury Compensation Program noted five cases of death from anaphylaxis after vaccinations [30]. Another study published in 2003 using electronic health record databases found that after 7644,049 doses of vaccination in children and adolescents, there were five possible cases of vaccine associated anaphylaxis and none resulted in death [29]. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends screening patients for contraindications and precautions, including allergy history, prior to vaccination [31]. However, since anaphylaxis following vaccination is not always predictable or preventable, ACIP also recommends that healthcare providers

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