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Review

Deaths following vaccination: What does the evidence show?

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ABSTRACT

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 from case reports in the media, is not a scientifically valid practice.

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1. Background

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 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].

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 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

Abbreviations: ACIP, 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.

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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 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 two 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 one or two 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 7,644,049 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 be prepared to treat medical emergencies including anaphylaxis if they occur [31].

4.2. Severely immunocompromised persons receiving live vaccines

Live vaccine viruses are attenuated so they do not cause infection in individuals with intact immune systems. Live vaccines,

however, are contraindicated for people who are severely immunocompromised [31] since their weakened immune systems may result in the live vaccine causing illness. Two published case reports describe immunocompromised children who received varicella vaccine, and where vaccine strain *varicella zoster* virus infection contributed to their deaths [32,33]. In one case, a 4-year-old child who had been in complete remission from acute lymphoblastic leukemia for five months received varicella vaccine during a 2-week break from chemotherapy [32]; in the other case, a 15-month-old did not have a diagnosis of being immunocompromised, but had failure to thrive and several hospitalizations beginning at five months of age for infections and respiratory problems requiring steroid treatment [33], indicating a possible undiagnosed immunodeficiency. There are at least six case reports of death among severely immunocompromised persons that have been linked to vaccine strain measles virus infection [34], including a case of vaccine associated pneumonitis in an immunocompromised person with HIV [35] and a case of measles inclusion-body encephalitis in a 21-month-old child with primary immunodeficiency [36]. CDC recommends screening prior to vaccination so that contraindications and precautions, including previously diagnosed immune system problems are identified [31].

4.3. Intussusception after rotavirus vaccine

Intussusception is a rare medical condition in which the bowel folds in, or telescopes, on itself. It can resolve on its own, but might also require medical treatment or in some cases surgery. In very rare instances, it can result in death (less than 1% of cases in developed countries) [37]. RotaShield®, the first licensed rotavirus vaccine, was withdrawn from use in 1999 after a greater than expected number of reports of intussusception were detected in post-marketing surveillance [38]. The attributable risk of intussusception was estimated to be one case for every 4670–9474 infants vaccinated [39] and one intussusception death after RotaShield® was reported in the literature [40]. There is a small increased risk of intussusception associated with the rotavirus vaccines that are currently licensed and in use (RotaTeq® and Rotarix®), but the risk is substantially lower than for RotaShield® at approximately one case in 20,000–100,000 doses [41–43]. One study estimated that among a hypothetical 4.3 million US birth cohort followed to age five years, currently licensed rotavirus vaccines prevent 14 deaths, more than 53,000 hospitalizations and more than 169,000 emergency room visits; by comparison the vaccines are estimated to result in an excess of 0.2 deaths, 45 hospitalizations, and 13 short stay visits from vaccine associated intussusception [44]. A published review of VAERS reports for 2006–2012 for the two currently licensed rotavirus vaccines indicated two death reports from intussusception; however, definitive causal associations with vaccination were not established in either case [45].

4.4. Guillain–Barré syndrome after seasonal and 2009 H1N1 (pandemic) inactivated influenza vaccines

Guillain–Barré syndrome is a rare disorder in which a person's own immune system damages peripheral nerve cells, causing muscle weakness and sometimes paralysis [46]. Most people recover fully from Guillain–Barré syndrome, but some may have permanent nerve damage. Known risk factors for GBS include bacterial or viral infections, especially *Campylobacter jejuni* [47] and other infections causing diarrhea or respiratory illnesses [46]. Studies assessing the risk of Guillain–Barré syndrome after seasonal inactivated influenza vaccine since 1976 have shown either no risk or a small increased risk on the order of one to two cases per million doses administered [48], which is similar to the risk observed with the 2009 influenza A (H1N1) monovalent vaccine [49]. However, one study found the cumulative risk of GBS over the entire influenza season was lower in individuals that received 2009 H1N1 (pandemic) inactivated influenza vaccines compared to unvaccinated individuals, indicating that vaccination might prevent GBS cases [50]. Another study using electronic health record data from 2000 through 2009 found that among 38 confirmed or probable GBS cases that occurred within six weeks of seasonal inactivated influenza vaccine, two deaths occurred during a median follow-up time of 6½ months; in neither of the cases that resulted in death was a causal association established with vaccination [51]. Approximately 5% of Guillain–Barré syndrome cases are fatal [52], but given the indeterminate association between influenza vaccination and GBS, risk of death from vaccine-associated GBS would have to be considered theoretical.

4.5. Syncope (fainting) after vaccination leading to head trauma and death

The IOM concluded that the available evidence convincingly supports a causal relationship between the injection of a vaccine and syncope [53], although this relationship exists for any medical procedure involving a needle stick (e.g., blood draw). In a study on quadrivalent human papillomavirus vaccine among young women, 15% reported presyncope or syncope after the first dose [54]. Post-vaccination syncope can result in injuries including head trauma. A VAERS case report described an incident of death attributed to blunt head trauma following a fall secondary to vasovagal syncope that occurred several minutes after vaccination with hepatitis B vaccine [55]. Syncope is an acute event that typically occurs within 15 minutes of vaccination [56], and the Advisory Committee on Immunization Practices suggests a 15-minute observation period after vaccination, especially if the patient is an adolescent [31].

4.6. Yellow fever vaccine-associated viscerotropic and neurologic disease

A rare, serious reaction to yellow fever vaccine called yellow fever vaccine-associated viscerotropic disease has similar symptoms to yellow fever illness. Initial symptoms, which usually occur within one week of vaccination, are fever, along with feeling generally unwell, muscle pain, nausea, vomiting, and/or diarrhea. These symptoms can progress to multisystem organ failure and death. More than 60 cases worldwide have been reported to CDC and of those, 63% resulted in death [57]. The incidence of yellow fever vaccine-associated viscerotropic disease in the United States is 0.4 cases per 100,000 doses administered [57].

Another rare reaction to yellow fever vaccine is yellow fever vaccine-associated neurologic disease. This includes several conditions, such as meningoencephalitis (inflammation of the brain and its membranes), Guillain–Barré syndrome, acute disseminated encephalomyelitis (inflammation of the brain and spinal cord), and bulbar palsy (paralysis of the motor units of the cranial nerves). Less than one case per 100,000 vaccine doses administered is reported, and it is rarely fatal [57].

Both yellow fever vaccine-associated viscerotropic and neurologic disease are more common in persons aged 60 years or older [57], therefore age 60 years or older is a precaution to receiving this vaccine. In the United States, yellow fever vaccine is recommended only for travelers who plan to visit areas where the disease is present and for laboratory personnel who work with yellow fever virus [58].

4.7. Complications from smallpox vaccine

Serious adverse reactions and complications from smallpox vaccine can result in death in rare cases [59]. Based on historical

data, the death rate following smallpox vaccination is approximately one death per million persons receiving an initial dose and one death per four million among persons receiving another dose after the first dose [60]. Death has also occurred among non-vaccinated persons who had accidental contact with vaccination sites of vaccine recipients [60]. Reactions that can cause or contribute to death include eczema vaccinatum, progressive vaccinia, postvaccinal encephalitis, myocarditis, and dilated cardiomyopathy. Additionally, vaccination of pregnant women can cause fetal infection resulting in stillbirth or infant death [59,60]. Patients should be carefully screened for precautions and contraindications prior to receipt of smallpox vaccine [61]. In 2008, a new smallpox vaccine, ACAM2000™, replaced the previously used vaccine, Dryvax®. The data indicate that ACAM2000™ has a similar safety profile to Dryvax® [61,62]. Naturally occurring smallpox disease has been eliminated worldwide, and in the United States, smallpox vaccine is currently only given to military personnel and selected individuals that might be at high risk of exposure, such as laboratory scientists that work with smallpox or similar viruses [63].

4.8. *Vaccine-associated paralytic poliomyelitis from oral poliovirus vaccine*

Vaccine-associated paralytic poliomyelitis (VAPP) is a rare adverse reaction that can occur in a recipient of live oral poliovirus vaccine (OPV) or in a contact of a recipient of OPV [64]. It can occur in healthy persons and in persons with immune system abnormalities. OPV is no longer used in the Unites States and has been replaced with inactivated poliovirus vaccine, but OPV is still used in many parts of the world. A recent review puts the risk of VAPP at around 4.7 cases per million births with an estimated 498 cases annually worldwide [65]. VAPP can result in death, but this is rare [66]. In the United States, from 1980 to 1989 there were 80 VAPP cases reported and among these reported cases, two patients (3%) died within 60 days after onset of paralysis [67].

5. Conclusion

Vaccines are rigorously tested and monitored and are among the safest medical products we use. Millions of vaccinations are administered to children and adults in the United States each year. Serious adverse reactions are uncommon and deaths caused by vaccines are very rare. Healthcare providers can take specific actions to help prevent adverse reactions, including proper screening for contraindications and precautions and observing a 15-minute waiting period after vaccinating to prevent fall-related injuries from syncope. CDC and FDA continuously monitor the safety of US licensed vaccines. All serious VAERS reports, including reports of death, are reviewed. A report is considered serious if at least one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [68]. In addition, CDC and FDA scientists use statistical techniques to check for disproportional reporting in the VAERS database for deaths and other adverse events for individual types and brands of vaccines [69]. If CDC or FDA were to detect a potential new safety problem with MMR or any other US licensed vaccine, this “signal” would be further assessed and regulatory and/or public health action would be taken, if necessary.

With respect to the recent claims of deaths caused by MMR vaccine [5–7], drawing broad cause and effect conclusions between vaccination and deaths based on spontaneous reports to VAERS, some of which might be anecdotal or second hand, is not a scientifically valid practice. In fact, a review of the VAERS data reveals that many of the death reports for MMR vaccine involved children with serious preexisting medical conditions or were likely unrelated to vaccination (e.g., accidents). These complete VAERS reports and any accompanying medical records, autopsy reports and death certificates have been reviewed in depth by FDA and CDC physicians and no concerning patterns have emerged that would suggest a causal relationship with the MMR vaccine and death.

The evidence for the safety and effectiveness of vaccines routinely given to children and adults in the Unites States is overwhelmingly favorable. In the case of MMR vaccine, this includes preventing hundreds of potential measles-related deaths each year [34]. Any discussion of the true risks of vaccination should be balanced by acknowledgment of the well-established benefits of vaccines in preventing disease, disability and deaths from infectious diseases.

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