

Vaccination and 30-Day Mortality Risk in Children, Adolescents, and Young Adults

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abstract

OBJECTIVE: This study evaluates the potential association of vaccination and death in the Vaccine Safety Datalink (VSD).

METHODS: The study cohort included individuals ages 9 to 26 years with deaths between January 1, 2005, and December 31, 2011. We implemented a case-centered method to estimate a relative risk (RR) for death in days 0 to 30 after vaccination. Deaths due to external causes (accidents, homicides, and suicides) were excluded from the primary analysis. In a secondary analysis, we included all deaths regardless of cause. A team of physicians reviewed available medical records and coroner's reports to confirm cause of death and assess the causal relationship between death and vaccination.

RESULTS: Of the 1100 deaths identified during the study period, 76 (7%) occurred 0 to 30 days after vaccination. The relative risks for deaths after any vaccination and influenza vaccination were significantly lower for deaths due to nonexternal causes (RR 0.57, 95% confidence interval [CI] 0.38–0.83, and RR 0.44, 95% CI 0.24–0.80, respectively) and deaths due to all causes (RR 0.72, 95% CI 0.56–0.91, and RR 0.44, 95% CI 0.28–0.65). No other individual vaccines were significantly associated with death. Among deaths reviewed, 1 cause of death was unknown, 25 deaths were due to nonexternal causes, and 34 deaths were due to external causes. The causality assessment found no evidence of a causal association between vaccination and death.

CONCLUSIONS: Risk of death was not increased during the 30 days after vaccination, and no deaths were found to be causally associated with vaccination.

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Ms McCarthy designed data collection instruments, carried out initial analyses, led the cause of death working group, and drafted the initial manuscript; Ms McCarthy and Ms Gee participated in conceptualizing and designing the study; Ms McCarthy and Ms King coordinated data collection; Ms Gee, Drs Sukumaran, Duffy, Kharbanda, Baxter, Daley, Hechter, and McNeil, Mr Weintraub, Ms Irving, and Ms King reviewed and revised the manuscript; Dr Sukumaran and Mr Weintraub participated in the analyses; Drs Sukumaran, Duffy, Kharbanda, Baxter, Daley, Hechter, and McNeil and Ms Irving reviewed medical records and participated on the cause of death working group; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Isolated cases of deaths after vaccination in adolescents have been reported, although not causally linked to vaccination.

WHAT THIS STUDY ADDS: Risk of death was not increased during the 30 days after vaccination, and no deaths were found to be causally associated with vaccination.

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Isolated deaths in individuals who had previously received human papillomavirus (HPV) vaccine have been highly publicized by the media. In a recent example, an otherwise healthy 12-year-old girl in Wisconsin died after a preventive health visit at which quadrivalent HPV vaccine (4vHPV) vaccine was administered. Ultimately, the cause of death was determined to be diphenhydramine intoxication, ingestion of a lethal amount of antihistamine.¹ There has been a recent increase in the number of vaccines recommended for adolescents by the Advisory Committee on Immunization Practices. Before 2005, the only routinely recommended vaccine for adolescents was the tetanus and diphtheria booster.² Currently, the Advisory Committee on Immunization Practices routinely recommends tetanus, diphtheria, and acellular pertussis (Tdap), meningococcal, HPV, and influenza vaccines to adolescents.³⁻⁶ In addition to the routine vaccine recommendations, individuals 9 to 26 years of age may receive multiple other vaccines (eg, varicella, pneumococcal, hepatitis A or B) as catch-up doses or if they are in a high-risk group. With an increasing number of vaccines recommended for adolescents, and deaths after vaccination receiving considerable media attention, some young adults and parents of adolescents have safety concerns regarding vaccination, particularly the HPV vaccine.⁷⁻¹⁰

Although instances in which a modern vaccine was established to have caused death are rare,¹¹⁻¹⁶ it is imperative to thoroughly investigate any death occurring shortly after vaccination. Thorough reviews of death reports after vaccination are conducted in the Vaccine Adverse Event Reporting System (VAERS)^{17,18}; however, observational studies are lacking. In a prior Vaccine Safety Datalink (VSD) study describing

mortality rates after vaccination, we found mortality rates to be lower than those of the U.S. population, as well as evidence of the “healthy vaccinee effect,” a phenomenon in which individuals are more likely to receive a vaccine when they are relatively healthy.¹⁹⁻²¹

Because of the publicity surrounding deaths temporally associated with HPV and the paucity of studies examining deaths in adolescents after vaccination, we evaluated deaths after vaccines administered to individuals 9 to 26 years of age in the VSD. This study assesses the risk of death in the first 30 days after vaccination, describes the causes of death, and includes an evaluation of the potential association of vaccination and death among older children and young adults.

METHODS

The VSD is a collaborative project between the Centers for Disease Control and Prevention (CDC) and several integrated health care systems (sites), which monitors the safety of vaccines in the United States.^{22,23} The VSD captures comprehensive medical and vaccination histories for >9 million people annually, ~3% of the US population. The VSD uses electronic medical records and other administrative sources at each site to gather data on enrollees including demographics, vaccinations, and medical outcomes, including deaths.

VSD mortality files are updated annually and include data on the cause and date of death. The files include deaths of all members enrolled in the VSD at the time of death, and most sites also capture deaths occurring in the ≥ 2 years after the end of enrollment. Immediate, underlying, and contributory causes of death are included in the files and coded using the *International Classification of Disease, Revision 10* (ICD-10). The majority of the sites

receive cause and date of death information from state death records; however, the National Death Index, Social Security Administration, electronic medical records, and administrative sources, such as health plan membership information, are also sources of date and cause of death data. Site-specific algorithms are used for matching mortality information across these multiple data sources to capture each VSD enrollee death in the electronic data.

Study Population and Case Ascertainment

This study included data from the following 6 VSD sites across the United States: Group Health Cooperative, Kaiser Permanente Colorado, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Southern California Kaiser Permanente, and Marshfield Clinic. We used the VSD electronic health data to identify deaths among males and females 9 to 26 years of age using the participants' unique VSD study identification. All deaths occurring between January 1, 2005, and December 31, 2011 with any previous documented vaccination during an enrollment period were included. Institutional review board approvals and data use agreements were obtained from each participating VSD site.

Medical Record Review

The VSD sites conducted medical record reviews for all deaths that occurred 0 to 30 days after vaccination to confirm the date and cause of death from the electronic health data. A standardized medical record review form was used to collect data from medical records, and copies of hospital discharge summaries, recent medical encounters, death certificates, and any other related documents were included when available. The medical record review form included information on patient demographics, date and time of

death, cause of death, manner of death, location of death, date and time of vaccination, vaccines administered, and underlying medical conditions.

Causality Assessment

A team of CDC physicians (Drs McNeil, Duffy, and Sukumaran) each reviewed the completed medical record review forms and additional documents to confirm the cause of death and assess the causal relationship between death and vaccination. When information on the cause of death was incomplete, coroner's reports were requested. After review by each physician on the CDC team, if the cause of death or association with a vaccination remained unclear, a working group consisting of investigators from CDC and each VSD site further discussed the case. Established criteria for causality assessment were used, with events classified into 3 categories: consistent with a causal relationship between the death and vaccine, inconsistent with a causal association, or indeterminate (if the evidence was insufficient to confirm or rule out a causal relationship).^{24,25} For each case, a consensus approach was used by the working group to make a final determination of cause of death and causal association with vaccination.

Case-Centered Analysis

We evaluated the association between vaccination and death at the population level using the case-centered method, which has been described elsewhere.²⁶⁻³¹ The case-centered method adjusts for seasonal variation in mortality and vaccine administration. In the analytic dataset, we included deaths of individuals who had received ≥ 1 vaccination in the year before death. For each death, the observed vaccination status during the prespecified risk window of 0 to 30 days before death was

determined. We chose a 0- to 30-day risk window to include causes of death that would be biologically plausible with regard to vaccination; however, we also conducted a cluster analysis to identify any shorter or longer windows of interest using a scan statistic software program, Satscan.³² In our primary analysis, we compared the observed versus expected odds of receiving a vaccination in the prespecified risk window and estimated relative risk using logistic regression. The observed odds was defined as the deaths vaccinated inside (0 to 30 days) versus outside (31 to 365 days) the risk window. The expected odds were derived from a risk set including the proportion of the entire VSD population vaccinated inside versus outside the risk window. The risk set was compiled using individuals with the same age in years, gender, VSD site, and number of vaccines received as the deaths. The dependent variable indicated whether the case received a vaccination inside or outside the risk window. An offset term was included in the model so that the intercept term of the logistic regression model became an estimate of the log of the relative risk. The offset term was specified as the log of the expected odds of a death occurring in the risk window. We also tested age, sex, VSD site, and number of vaccines received before death for potential interaction.

In the primary analysis, we ascertained cause of death for all deaths after vaccination using the VSD mortality cause of death file. Deaths due to external causes such as automobile accidents, gunshot wounds, and other injuries were excluded (ICD-10 codes S00 to T98 and V01 to Y98). Deaths caused by suicide after vaccination were excluded from the primary analysis and examined independently to assess any possible association between vaccination and suicide. In a secondary analysis, we

included all deaths within 30 days of vaccination, regardless of cause, to take into account potential misclassification of cause of death. We planned separate analyses for deaths caused by syncope on the day of vaccination, since this is one of the rare instances when a death can be attributed to a vaccine.¹¹ In addition, we estimated the relative risk of death after specific vaccines, including 4vHPV, influenza vaccine, Tdap, hepatitis A and B vaccines, varicella vaccine, meningococcal conjugate quadrivalent vaccine, and pneumococcal conjugate (7-valent) and polysaccharide (23-valent) vaccines. We chose to focus the analysis of human papillomavirus vaccines on 4vHPV, as 99% of the vaccine used in the United States is of the quadrivalent form.³³

RESULTS

From January 1, 2005, to December 31, 2011, there were 1100 deaths identified within 12 months after any vaccination among 2 189 504 VSD enrollees 9 to 26 years of age. Of the deaths identified, the mean number of days between vaccination and death was 179; only 76 deaths (7%) occurred 0 to 30 days after vaccination. Sixty deaths (79%) followed receipt of 1 vaccine in the vaccine visit before death, 11 (14%) 2 vaccines, 2 (3%) 3 vaccines, and 3 (4%) ≥ 4 vaccines. During the cluster analysis, no significant clusters of deaths were found in 0 to 365 days, so we conducted analyses for the predetermined 0- to 30-day risk window only.

Figure 1 summarizes the causes of death confirmed by medical record review for the 76 deaths that occurred during days 0 to 30 after vaccination. The cause and date of death was derived from the state death certificate but unable to be confirmed in the medical record for 17 individuals. Fifteen of those were listed as deaths due to external

causes (suicides, homicides, or accidents), and 1 death was due to cardiac arrhythmia. We found 1 death with no evidence of death in the medical record, only mention of the date of death in the electronic health data. Of the remaining 59 deaths, 1 cause of death was unknown, 25 deaths were due to nonexternal causes, and 34 deaths were due to external causes.

The results of the case-centered analysis evaluating the risk of death after vaccination are summarized in Table 1. The relative risks for death 0 to 30 days after any vaccination and after influenza vaccination were significantly lower for deaths due to nonexternal causes and deaths due to all causes. When examined independently, no other individual vaccines were significantly associated

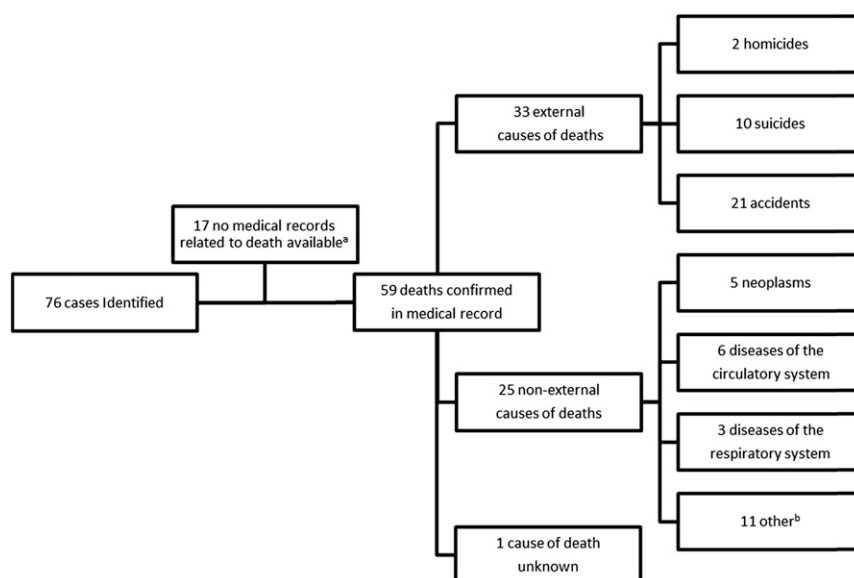


FIGURE 1 Causes of death for deaths occurring on days 0 to 30 after vaccination among individuals 9 to 26 years of age in the VSD, 2005 to 2011. ^aCause and date of death derived from state data. ^bAddison disease, Rett syndrome, cerebral palsy, Takayasu disease, aplastic anemia, grand mal seizure, diabetes, obstetric cause, congenital malformation of heart, septic shock, and morbid obesity.

TABLE 1 Case-Centered Analysis of the Association Between Death and Vaccination Among Individuals 9 to 26 years of Age in the VSD, 2005–2011

Vaccine Type	Total Deaths	Deaths Days 0–30 After Vaccine	Relative Risk	95% Confidence Interval	Vaccine Doses Administered
Deaths due to nonexternal causes					
Any vaccine	508	28	0.57 ^a	0.38–0.83	8 472 685
4vHPV	34	4	1.28	0.44–3.68	1 355 535
Influenza	340	14	0.44 ^a	0.24–0.80	2 289 807
Tdap	75	4	0.38	0.12–1.23	1 470 934
Hepatitis A and B	46	2	0.48	0.11–1.98	876 209
Varicella	21	1	0.38	0.05–2.89	666 395
MCV4	36	1	0.29	0.04–2.11	1 128 721
Pneumococcal	37	5	0.94	0.31–2.82	23 358
Deaths due to all causes					
Any vaccine	1100	76	0.72 ^a	0.56–0.91	8 472 685
4vHPV	117	13	1.12	0.62–2.03	1 355 535
Influenza	582	28	0.42 ^a	0.28–0.65	2 289 807
Tdap	249	23	0.87	0.56–1.35	1 470 934
Hepatitis A and B	136	7	0.58	0.27–1.24	876 209
Varicella	51	4	0.70	0.24–2.00	666 395
MCV4	114	8	0.77	0.37–1.60	1 128 721
Pneumococcal	50	7	1.03	0.44–2.44	23 358

MCV4, meningococcal conjugate quadrivalent vaccine; Pneumococcal, pneumococcal conjugate (7-valent) and polysaccharide (23-valent) vaccines.

^a Statistically significant result ($P < .05$).

with death. Table 1 also includes the number of vaccinations received during the study period for reference.

We found only 1 death on the day of vaccination, which was not related to syncope; therefore, no separate analyses on syncope-related deaths were conducted. We

found no significant interaction for age, gender, site, or number of vaccines received. Of the 15 deaths by suicide, 3 occurred after influenza vaccination, with a relative risk of 0.26 (95% confidence interval 0.07–0.94).

Of the 59 deaths with medical records available for review, the

team of CDC physicians confirmed the cause of death in 53 cases and found no relationship between vaccination and death. Three cases were reviewed by the VSD causality assessment working group with uncertain causes of death or an uncertain relationship between death and the vaccine. The first case

received tetanus and 4vHPV vaccines 14 days before death, and the cause of death given by the coroner was thoracic aortic dissection. With the evidence provided, the working group determined the cause of death to be inconsistent with a causal association between the vaccines received and death. The second case received Tdap and 4vHPV vaccines 11 days before death, and the cause of death given by the coroner was unknown. Without a cause of death, the working group determined the relationship between the vaccines and death to be indeterminate because of a lack of information to confirm or rule out a causal association. The third case received 4vHPV vaccine 18 days before death, and the cause of death listed in the patient's medical record and coroner's report was sepsis of unknown etiology. The working group categorized the cause of death in this case as indeterminate because of a lack of a confirmed etiology of sepsis and, therefore, lack of evidence to confirm or rule out a causal association.

DISCUSSION

In this study, we examined causes of death after vaccination, and evaluated the association between vaccination and death. Over the 7-year study period, after the administration of 8 472 685 vaccines, we did not find any deaths in the 0- to 30-day window after vaccination beyond what was expected. In fact, the risk of death 0 to 30 days after any vaccine was decreased, regardless of cause of death.

Recently, deaths immediately after 4vHPV vaccination have garnered intense media attention. Often, these media stories do not take into account the background rates of death in older children and young adults or disclose the potential for non-vaccine-related causes of death. In our study, 13 deaths were

identified after 4vHPV vaccine among individuals 9 to 26 years of age within the 0- to 30-day risk window, a rate of 11.7 deaths per 100 000 person-years. This is significantly lower than what would be expected in this age group regardless of vaccination. The National Center for Health Statistics found the 2011 death rate for all causes among persons 15 to 24 years to be 67.6 deaths per 100 000 people.³⁴

We were able to examine the medical records and adjudicate the cause of death for 58 of the 76 deaths that occurred in the risk window. Of these, more than half were due to external causes: homicides, suicides, or accidents. This is expected, given these are among the most common causes of death for adolescents and young adults.³⁵ We did not find any deaths causally associated with 4vHPV or any other vaccination; however, 2 deaths were found to be indeterminate in the review by the working group. One death was caused by sepsis with uncertain etiology. Because the source of the sepsis was unclear, the working group could not provide a definitive cause of death. However, there have not been any previous studies indicating that a nonlive vaccine has the potential to cause sepsis, and there was no indication that the vaccine was involved in this case. The autopsy findings for the second death did not offer an explanation for the cause of death; however, the coroner noted that in all probability the death was due to cardiac arrhythmia without an anatomic basis. Sudden deaths such as this, although uncommon, do occur in this population, regardless of vaccination history.³⁶⁻³⁸

VAERS monitors the safety of all vaccinations, including 4vHPV.³⁹ From June 2006 to March 2013, 96 reports of death after receipt of 4vHPV vaccine were submitted to VAERS. Detailed review of every report of death after 4vHPV

identified no pattern of occurrence of death or diagnosis at death that would suggest a causal association with 4vHPV.⁵ The current VSD study provides additional assurance to the VAERS findings that deaths after 4vHPV vaccination are likely only temporally and not causally associated with the vaccine.

Our study is subject to certain limitations. Seventy-five percent of individuals in our study who died of nonexternal causes had significant comorbidities, making them more likely to be indicated for influenza and other vaccines for high-risk groups. However, vaccination would be less probable in these individuals if death was imminent. Although this may not be bias from the traditional healthy vaccinee effect, as our population was relatively unhealthy, there is potential for unmeasured confounding related to the timing of vaccination by indication or disease severity. In our study, there appears to be a decreased risk of death after influenza vaccine and any vaccine. During the analysis, we also observed a similar effect in deaths due to external causes (accidents, suicides, and homicides) after influenza vaccination (relative risk 0.42, 95% confidence interval 0.23 to 0.76), which are very unlikely to be influenced by history of vaccination. This illustrates the magnitude of bias, and although we recognize that confounding may be present, it is unlikely to be masking a true association between vaccination and death.

We were unable to confirm cause of death in the medical record for 17 (22%) of the deaths. Fifteen were due to external causes according to the state death certificate data. It is likely that these individuals died outside of the health care system and thus the deaths were not captured in the health plan's medical record. Additionally, we had a relatively small sample size, particularly when examining individual vaccines

independently. We were able to capture deaths only through 2011 because of the reliance on vital statistics data and the lag associated with obtaining those data from the states. Additional years of data would provide a larger sample for examining specific vaccines. Also, a small percentage of deaths may not have been captured, if for instance a health plan member ceased membership and died in another state. However, capturing deaths ≤ 2 years postenrollment should overcome this in part, as our ascertainment of death did not rely solely on state death records. Finally, we studied the increased risk of death only in the 30 days postvaccination; our study was not designed to look at any potential increased risk of death that could occur months or years after vaccination.

CONCLUSIONS

To our knowledge, this study currently represents the largest population-based epidemiologic investigation of the association between vaccination and death among individuals 9 to 26 years of age. Although there has been significant research conducted on deaths after vaccination in both infants and older adults, this study fills a void by investigating deaths among older children and young adults.^{26,40–44} We assessed deaths after vaccination on a population level as well as an individual level to provide a complete evaluation of vaccine safety with regard to death. This research should reassure the public with regard to the safety of 4vHPV vaccine, as well as other vaccines routinely administered to individuals 9 to 26 years of age.

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ABBREVIATIONS

4vHPV: quadrivalent HPV vaccine
CDC: Centers for Disease Control and Prevention
HPV: human papillomavirus
ICD-10: *International Classification of Disease, Revision 10*
Tdap: tetanus, diphtheria, and acellular pertussis
VAERS: Vaccine Adverse Event Reporting System
VSD: Vaccine Safety Datalink

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