Mortality Rates and Cause-of-Death Patterns in a Vaccinated Population

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Background: Determining the baseline mortality rate in a vaccinated population is necessary to be able to identify any unusual increases in deaths following vaccine administration. Background rates are particularly useful during mass immunization campaigns and in the evaluation of new vaccines.

Purpose: Provide background mortality rates and describe causes of death following vaccination in the Vaccine Safety Datalink (VSD).

Methods: Analyses were conducted in 2012. Mortality rates were calculated at 0–1 day, 0–7 days, 0–30 days, and 0–60 days following vaccination for deaths occurring between January 1, 2005, and December 31, 2008. Analyses were stratified by age and gender. Causes of death were examined, and findings were compared to National Center for Health Statistics (NCHS) data.

Results: Among 13,033,274 vaccinated people, 15,455 deaths occurred between 0 and 60 days following vaccination. The mortality rate within 60 days of a vaccination visit was 442.5 deaths per 100,000 person-years. Rates were highest in the group aged ≥85 years, and increased from the 0–1-day to the 0–60-day interval following vaccination. Eleven of the 15 leading causes of death in the VSD and NCHS overlap in both systems, and the top four causes of death were the same in both systems.

Conclusions: VSD mortality rates demonstrate a healthy vaccinee effect, with rates lowest in the days immediately following vaccination, most apparent in the older age groups. The VSD mortality rate is lower than that in the general U.S. population, and the causes of death are similar.
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Introduction

Public concern about adverse events following immunization, especially deaths, can cause disruption in immunization programs, resulting in an increase in the morbidity and mortality of vaccine-preventable diseases.[1,2] In 2009, a Japanese study found 107 deaths following H1N1 influenza A vaccination using a passive surveillance system. The study assumed causality between the vaccine and deaths without any evaluations of background rates.[3] In a letter to the editor, McNeil et al. pointed out that passively reported data generally cannot be used to assess causality. In addition, the expected number of deaths in Japan following an estimated 15 million doses of H1N1 vaccine administered would be >8000 deaths during the 20 days

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following vaccination, based on the crude mortality rate. This number is substantially greater than the 107 reported deaths.[4] This example is a case in which background mortality rates following vaccination could have been used to interpret the deaths more accurately.

Determining the baseline mortality rate in a vaccinated population is necessary to be able to identify any unusual increases in deaths following vaccine administration. Although the current body of evidence does not suggest a causal relationship between vaccines and death, it is important to provide background rates of mortality to aid in the assessment of vaccine safety concerns. Background rates are particularly useful in the evaluation of new vaccines, and during mass immunization campaigns in addition to vaccine safety surveillance efforts.[5] Black et al. examined the importance of background rates of disease and mortality in assessing vaccine safety. They highlighted the value of background rates as a crucial tool for separating legitimate vaccine safety concerns from events that are temporally associated with, but not caused by, vaccination.[6]

Although countries such as the U.S. routinely publish national mortality rates based on vital statistics data, these published rates may not be useful for vaccine safety evaluations because vaccinated individuals tend to be in generally good health and may have lower mortality rates than the general population. Thus, baseline mortality rates after vaccine administration are needed to better evaluate the safety of new vaccines. The present study provides background mortality rates following vaccination of any type in the Vaccine Safety Datalink (VSD), a medically insured U.S. population. In addition, the study describes the cause of death patterns, and examines mortality rates by age, gender, and number of days following vaccination.

Methods

The VSD is a collaborative project between the CDC and ten MCOs that conduct vaccine safety research and surveillance.[7] All of the VSD MCOs participated in the current study: Group Health Cooperative (Seattle WA); Kaiser Permanente Colorado (Denver CO); Kaiser Permanente Northwest (Portland OR); Harvard Vanguard Medical Associates, and Harvard Pilgrim Health Care (Boston MA); HealthPartners (Minneapolis–St. Paul MN); Northern California Kaiser Permanente (Oakland CA); Southern California Kaiser Permanente (Pasadena CA); Kaiser Permanente Georgia (Atlanta GA); Kaiser Permanente Hawaii (Honolulu HI); and Marshfield Clinic (Marshfield WI). IRBs at CDC and each VSD site approved the study and agreed that informed consent was not required. Analyses were conducted in 2012.

The VSD captures comprehensive medical and immunization histories for more than 10 million people annually, or approximately 3% of the U.S. population. The VSD uses administrative and other sources at each MCO to gather data on enrollee demographics, vaccination, and medical outcomes, including mortality. The VSD conducts planned immunization safety studies following the introduction of new vaccines or changes in the immunization schedule, as well as timely investigations of hypotheses that arise from review of medical literature, clinical case reports, or reports from the Vaccine Adverse Event Reporting System (VAERS), a national passive adverse-event reporting system.[8]

Vaccine Safety Datalink mortality files are updated annually and include data on cause and date of death. The files include deaths of all members enrolled in the VSD and deaths occurring in the 2 years or more following the end of enrollment, depending on the site. The majority of the MCOs 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 information. Each site uses different algorithms for matching mortality information across the multiple data sources; however, each site exhausts all resources to capture each VSD enrollee death.

Vaccine Safety Datalink mortality files include the immediate, underlying, and contributory causes of death coded using the ICD-10. The current study used the underlying cause of death for analyses. The underlying cause is defined by the WHO as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury."[9]

The study cohort included adults and children in the VSD who were vaccinated with at least one vaccine between January 1, 2005, and December 31, 2008. Participants were required to be enrolled in the VSD at the time of vaccination to ensure that any death following the vaccination would be captured. The vaccinated cohort was linked with records in the VSD mortality database using the unique VSD study identification number (ID). Individuals with a recorded date of death within 60 days following vaccination were included in the cohort.

Cause of death in VSD was categorized by body system in order to describe the causes of death following vaccination. The 2008 National Vital Statistics report on U.S. deaths from the National Center for Health Statistics (NCHS) classifies causes of death from ICD-10 codes into 113 selected causes of death.[10] These classifications were used to group the causes of death following vaccination in the VSD in addition to the body system classifications. Some ICD-10 codes found in the VSD data were not listed in the NCHS classifications for the 113 selected causes; in this case, an additional category was created for the death using the ICD-10 classification.

The percentage of total deaths, crude death rates, and age-adjusted death rates were calculated for the 15 leading causes of death. All age-adjusted rates were based on a direct age adjustment using the 2000 U.S. standard population.[11] For comparisons to NCHS, mortality rates and leading causes of death were obtained from the 2008 death data published in the National Vital Statistics Report.[10]

Mortality rates for deaths occurring within the following intervals after a vaccination visit were calculated: 0–1 day, 0–7 days, 0–30 days, and 0–60 days (Day 0 was the day of vaccination visit) for all ages. These intervals were chosen in order to examine possible healthy vaccinee effects,[12] as well as to provide background rates from varying intervals for potential use in future surveillance activities. For each interval, only vaccines given with enough follow-up time to capture the death were included. For example, for deaths within 60 days of a vaccination visit, only vaccinations administered through November 1, 2008, were included.

A secondary analysis was conducted for children aged 0–18 months; the analysis was limited to the time intervals through 30 days, and a death rate for the 60-day interval was not calculated, because of the short time intervals between the recommended infant immunizations.[13] The number of deaths by the number of days following vaccination was described for various ages using bar graphs to examine possible healthy vaccinee effects. For this analysis, the age groups were collapsed into 0–24 years, 25–64 years, and ≥65 years.[12]

Rates were calculated using both person-years and vaccination visits as a denominator. Person-days were converted to person-years so that mortality rates would be easier to interpret, particularly when making comparisons to NCHS rates that are calculated per 100,000 people per year. For the person-time calculation, each vaccinated person contributed a maximum of 2 days, 8 days, 31 days, or 61 days of person-time for each vaccination visit unless they were censored by death or another vaccination event, in which case person-time accrued up to the date of the censoring event.

The analyses were stratified by gender and the following age groups: <1 year, 1–4 years, 5–10 years, 11–24 years, 25–64 years, 65–74 years, 75–84 years, and ≥85 years. For children aged 0–18 months, age groups were created based on the vaccination schedule: <1 month, 1–2 months, 3–4 months, 5–8 months, 9–13 months, 14–16 months, and 17–18 months.[13] Finally, the number of deaths by the number of days following vaccination was described for various ages using bar graphs to examine possible healthy vaccinee effects. For this analysis, the age groups were collapsed into 0–24 years, 25–64 years, and ≥65 years.[12]

Results

Among 13,033,274 people vaccinated with at least one vaccine, there were 17,108,478 vaccination visits with 24,842,470 total vaccines administered in the VSD between January 1, 2005, and December 31, 2008. There were 116,043 deaths, of which 15,455 (13%) occurred between 0 and 60 days following vaccination. There were 6738 (6%) deaths within 30 days; 1021 (1%) within 7 days; and 132 (0.1%) within 1 day of a vaccination visit. The mean number of days between a vaccination visit and death was 269, median was 218, mode was 56, and range was 0–1419.

Deaths within 60 days of a vaccination visit occurred mostly in November (30%) and December (33%), and were lowest in the spring and summer months (April–September). The majority of vaccines were administered in October (27%) and November (16%), with the remainder dispersed evenly throughout the rest of the year. This distribution of vaccines was driven by influenza vaccine administration.

The overall age-adjusted death rate within 60 days of a vaccination visit was 442.5 deaths per 100,000 person-years in the VSD from 2005–2008 (crude rate: 608 deaths per 100,000 person-years). In 2008, the age-adjusted death rate in NCHS was 758.3 per 100,000 people (crude rate: 813 deaths per 100,000 people), significantly higher than the VSD mortality rate ($p < 0.0001$). Table 1 shows the 15 leading causes of death for the VSD within 60 days of a vaccination visit, compared with the 15 leading causes of death from NCHS data; 11 of the 15 leading causes overlap in both systems, and the top four causes of death were ranked the same in both systems. Approximately 7% of the causes of death in the VSD were unknown and therefore not included in the ranking.

In the overall distribution of cause of death classified by body system among all ages, the categories that represent the majority of the distribution include diseases of the circulatory system (32%); neoplasms (24%); and diseases of the respiratory system (10%). In children aged 0–18 months, congenital malformations, deformations, and chromosomal abnormalities (22%) were the leading cause of death within 30 days of a vaccination visit; sudden infant death syndrome (SIDS) was the second-leading cause of death (16%). The leading cause of death within 60 days of a vaccination visit in children aged <18 years was external causes of morbidity and mortality (21%); next in leading causes of death were congenital malformations, deformations, and chromosomal abnormalities (18%), and SIDS (13%).

Mortality rates by age and gender are shown in Table 2. Mortality rates were highest in the oldest age group (≥85 years). Among all ages, the mortality rate increased from 141.0 deaths per 100,000 person-years during the 0–1-day interval to 608.23 deaths per 100,000 person-years during the 0–60-day interval following vaccination. This pattern of an increase in the mortality rates as the length of the post-vaccination time interval increases was less apparent in the younger age groups. Among children aged <18 months, mortality rates also increased from the 0–1-day to the 0–30-day interval following vaccination, except in children aged <1 month (Table 3). Children aged <1 month had the highest mortality rate, and the rate decreased as the time interval following vaccination increased.

Figure 1 shows the number of deaths by the number of days following vaccination for various age groups: 0–24 years, 25–64 years, and ≥65 years. The total number of deaths in each age group was 362, 2,662, and 12,429, respectively (age was unknown for two of the cases). The number of deaths increased as the number of days following vaccination increased in the age groups of 25–64 years and ≥65 years. The pattern is most apparent in the oldest group. The age group of 0–24 years did not follow the same pattern.

Discussion

Generally, people are more likely to receive a vaccine when they are in a relatively healthy, disease-free state,

Table 1. Fifteen leading causes of death: NCHS and VSD

Rank	NCHS: 2008	VSD: 2005–2008[a] (within 60 days following a vaccination visit)
1	Diseases of the heart	Diseases of the heart
2	Malignant neoplasms	Malignant neoplasms
3	Chronic lower respiratory tract diseases	Chronic lower respiratory tract diseases
4	Cerebrovascular diseases	Cerebrovascular diseases
5	Accidents (unintentional injuries)	Diabetes mellitus
6	Alzheimer's disease	Alzheimer's disease
7	Diabetes mellitus	Accidents (unintentional injuries)
8	Influenza and pneumonia	Influenza and pneumonia
9	Nephritis, nephrotic syndrome, and nephrosis	Mental and behavioral disorders[b]
10	Intentional self-harm (suicide)	Other diseases of the respiratory system
11	Septicemia	Nephritis, nephrotic syndrome, and nephrosis
12	Chronic liver disease and cirrhosis	Chronic liver disease and cirrhosis
13	Essential hypertension and hypertensive renal disease	Essential hypertension and hypertensive renal disease
14	Parkinson's disease	Other diseases of the intestines[b]
15	Assault (homicide)	Parkinson's disease

[a]Year 2008 data from one VSD site were not included, because of incomplete information.
[b]Classified using ICD-10 categories
NCHS, National Center for Health Statistics; VSD, Vaccine Safety Datalink

and the VSD mortality rates demonstrate this healthy vaccinee effect.[12] Based on this phenomenon, lower mortality rates would be expected in the days immediately following vaccination rather than in days farther along in time, such as the 0–60-day interval. A lower number of deaths occurred in the days immediately following vaccination in the older age groups, and death on the day of vaccination was rare (Figure 1).

In fact, the number of deaths within the first few days following vaccination is less than half the number seen in 30 days or more following vaccination. Although this effect was not as distinct in the age group of 0–24 years, the overall low number of deaths in this group may account for the irregular trend. Deaths in infants aged less than 1 month also are included in this group and did not demonstrate the healthy vaccinee effect when analyzed independently. Additionally, the healthy vaccinee effect may be associated with influenza and pneumococcal vaccinations given to older age groups more so than pediatric vaccines.[14]

For children aged less than 1 month, the death patterns observed in VSD are consistent with NCHS; most neonatal deaths occur within 24 hours after birth.[15] The natural age distribution of death in the days following birth, combined with the timing of the recommendation for the first dose of hepatitis B vaccine soon after birth, represents a unique situation that results in a very different pattern of mortality following vaccination than that seen in any other age group.[16] For this reason, the healthy vaccinee effect would not be observed. These factors present a challenge in evaluating patterns of death following vaccine given soon after the time of birth.

The majority of the deaths following vaccination in the VSD occurred in the winter months, which is in accordance with general mortality trends.[17–19] The overall age-adjusted mortality rate following vaccination was lower in VSD than in the general population represented by NCHS data. There may be a number of factors contributing to the lower mortality rate. The VSD is an exclusively insured population, so it might be expected to have access to better healthcare than the total U.S. population. As insurance is often linked to employment, the healthy worker effect also may be contributing to the lower mortality rates for families in VSD. Individuals must be healthy enough to be employable, and therefore have a mortality risk that is initially lower than the general population average.[20,21]

Overall, the patterns of cause of death are similar in the VSD population and the general U.S. population (Table 1). Suicide and homicide were not in the leading 15 causes of death for VSD, which may be related to

Table 2. VSD mortality rates following vaccination, all ages (per 100,000 person-years and per 100,000 vaccination visits)

		Age (years)																	
		<1		1–4		5–10		11–24		25–64		65–74		75–84		≥85		All	
Interval (days)	Gender	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits
0–1	Both	114.62	0.63	0.00	0.00	0.00	0.00	13.86	0.08	84.36	0.46	264.22	1.45	376.27	2.06	2075.63	11.36	141.00	0.77
	Female	78.73	0.43	0.00	0.00	0.00	0.00	11.31	0.06	52.46	0.29	174.53	0.96	252.70	1.38	1719.65	9.41	103.23	0.57
	Male	148.47	0.81	0.00	0.00	0.00	0.00	17.89	0.10	130.21	0.71	369.81	2.02	532.54	2.92	2653.96	14.53	188.83	1.03
0–7	Both	102.37	2.24	18.58	0.41	0.00	0.00	13.93	0.30	141.21	3.09	516.22	11.28	1061.42	23.20	3804.11	83.12	273.82	5.99
	Female	98.87	2.16	14.31	0.31	0.00	0.00	11.38	0.25	90.99	1.99	376.60	8.23	901.07	19.69	3298.75	72.09	223.19	4.88
	Male	105.67	2.31	22.64	0.50	0.00	0.00	17.97	0.39	213.37	4.66	680.60	14.87	1264.22	27.62	4625.48	101.03	337.93	7.39
0–30	Both	115.19	9.65	15.54	1.30	4.39	0.37	15.32	1.28	224.71	18.77	845.56	70.38	2174.82	181.73	6755.70	564.94	481.83	40.28
	Female	108.98	9.13	16.59	1.39	4.51	0.38	12.15	1.02	165.46	13.82	679.30	56.55	1762.99	147.40	6075.84	508.49	410.50	34.31
	Male	121.05	10.14	14.55	1.22	4.27	0.36	20.30	1.70	310.02	25.89	1041.65	86.69	2696.29	225.16	7852.28	655.80	572.05	47.83
0–60	Both	103.05	16.23	17.65	2.82	7.28	1.19	19.34	3.14	279.19	45.06	1089.25	175.22	2819.19	457.30	8440.27	1371.41	608.23	97.99
	Female	88.33	13.93	18.11	2.89	3.74	0.61	13.97	2.26	201.75	32.57	855.57	137.69	2308.98	374.96	7587.21	1234.51	514.39	82.90
	Male	116.95	18.41	17.21	2.75	10.62	1.73	27.78	4.53	390.66	63.02	1365.50	219.54	3465.36	561.32	9817.19	1591.58	726.99	117.09

Note: Interval indicates days following vaccination. Visits indicates vaccination visits.
VSD, Vaccine Safety Datalink

socioeconomic factors.[22,23] Also, the unknown causes of death in the VSD may account for some minor variations between these systems. When the causes of death were classified by body system, the most common causes of death for all ages were still consistent with NCHS. Death rates were highest in men/boys; the oldest age groups; and children, particularly the age group of less than 1 year. These trends are also consistent with national statistics.[10]

Limitations and Strengths

Unlike the VSD, which can provide mortality rates for a well-described and documented population, VAERS must rely on voluntarily reported deaths after vaccination. The VSD and VAERS cannot be compared directly because VAERS is a passive reporting system and may have incomplete information. VAERS also does not have data for the number of vaccines administered and therefore cannot calculate adverse event rates; however, reporting rates are often calculated.[8]

Background mortality rates in a large vaccinated population can be helpful in interpreting data from VAERS.[24] For example, mortality reporting rates following a specific vaccine in VAERS can be compared with background rates in VSD to assist in assessing a possible increased risk. Assessments such as these need to be interpreted with caution, as VAERS is subject to biased reporting (underreporting, or stimulated reporting).

Mortality data were provided through 2008 only, because of the reliance on vital statistics data and the lag associated with obtaining those data from the states, and cause of death information was missing for approximately 7% of deaths in the cohort. A small percentage of deaths may not have been captured (e.g., if a health plan member ceased membership and died in another state). Additionally, because the VSD is an insured population, the mortality rates may not be completely generalizable to the U.S. population. However, the leading causes of

Table 3. VSD mortality rates following vaccination, 0–18 months (per 100,000 person-years and per 100,000 vaccination visits)

Interval (days)	Gender	Age (months) <1		1–2		3–4		5–8		9–13		14–16		17–18		All	
		Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits	Person-years	Visits
0–1	Both	551.61	3.02	54.25	0.30	55.03	0.30	40.38	0.22	0.00	0.00	0.00	0.00	0.00	0.00	77.66	0.43
	Female	377.06	2.06	0.00	0.00	113.41	0.62	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	53.27	0.29
	Male	717.80	3.93	105.47	0.58	0.00	0.00	78.38	0.43	0.00	0.00	0.00	0.00	0.00	0.00	100.72	0.55
0–7	Both	415.54	9.09	68.09	1.49	69.07	1.51	40.59	0.89	10.35	0.23	0.00	0.00	0.00	0.00	71.53	1.56
	Female	331.42	7.25	84.12	1.84	113.89	2.49	20.92	0.46	21.27	0.47	0.00	0.00	0.00	0.00	71.36	1.56
	Male	495.60	10.85	52.96	1.16	26.84	0.59	59.10	1.29	0.00	0.00	0.00	0.00	0.00	0.00	71.69	1.57
0–30	Both	278.89	23.61	144.62	12.12	106.33	8.93	46.34	3.86	16.79	1.39	24.73	2.06	16.10	1.34	83.51	6.98
	Female	298.51	25.27	111.73	9.37	105.76	8.88	44.94	3.74	11.50	0.96	25.31	2.10	33.17	2.77	79.93	6.68
	Male	260.26	22.03	175.65	14.72	106.88	8.97	47.66	3.96	21.81	1.81	24.18	2.01	0.00	0.00	86.90	7.26

Note: Interval indicates days following vaccination. Visits indicates vaccination visits.
VSD, Vaccine Safety Datalink

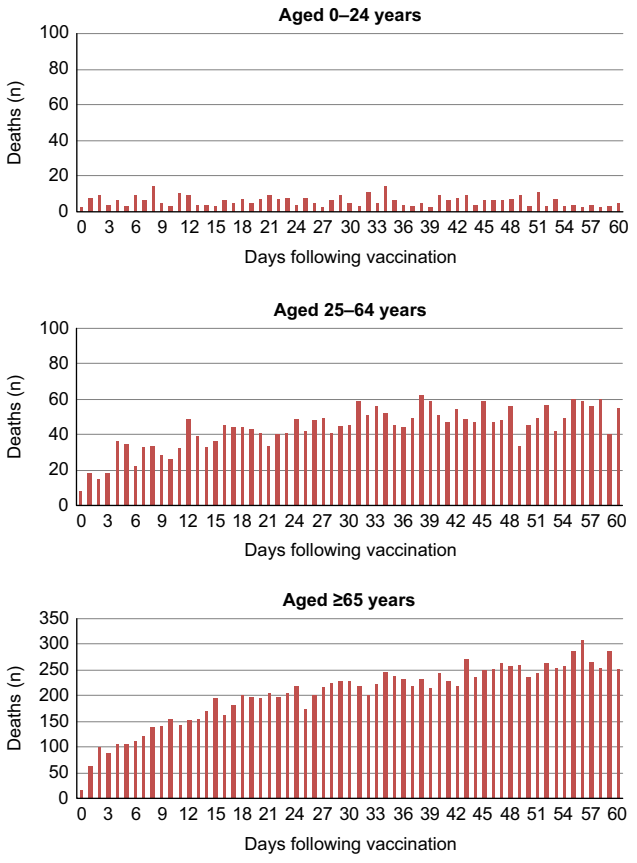

Figure 1. Number of deaths by day following vaccination in the Vaccine Safety Datalink: 2005–2008

death in both populations were found to be similar. The strengths of this study are the large sample size, and the fact that mortality rates could be obtained for a well-defined vaccinated population.

Conclusion

Prior to this study, the VSD did not have background mortality rates on its population readily available. The main finding from this study was the low mortality rates in the days immediately following vaccination, providing evidence of a healthy vaccinee effect. Although there is currently no evidence to support a causal relationship between vaccinations and death, this study provides background mortality rates following vaccination to be used as a baseline when examining the safety profiles of new vaccines, and during mass immunization campaigns.

Additionally, these background rates can be utilized in communications to the public regarding vaccine safety risks.[25,26] The VSD provides a vital infrastructure for monitoring vaccine safety, and generating background mortality rates is another asset of the vaccine safety system. Similar analyses should be conducted

when new vaccines are added to the ACIP recommended schedule, and also would be useful in other populations, including vulnerable subpopulations such as pregnant women and people with underlying health conditions.

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