Expected Rates of Select Adverse Events following Immunization for COVID-19 Vaccine Safety Monitoring

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Abstract Text Summary: Expected rates of 21 potential adverse events of special interest that would occur following COVID-19 vaccination within 1-, 7-, and 42-day intervals without causal associations are presented. These data are critical for vaccine safety monitoring, health communication, and benefit-risk assessment.

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 (CDC). Authors do not declare any conflict of interests or funding sources.

Abstract

Using meta-analytic methods, we calculated expected rates of 21 potential adverse events of special interest (AESI) that would occur following COVID-19 vaccination within 1-, 7-, and 42-day intervals without causal associations. Based on these expected rates, if 10,000,000 persons are vaccinated, 0.5, 3.7, and 22.5 Guillain-Barre syndrome cases; 0.3, 2.4, and 14.3 myopericarditis cases; and 236.5, 1655.5, and 9932.8 all-cause deaths would occur coincidentally within 1, 7, and 42 days post-vaccination, respectively. Expected rates of potential AESI can contextualize events associated temporally with immunization, aid in safety signal detection, guide COVID-19 vaccine health communications, and inform COVID-19 vaccine benefit-risk assessments.

Key words: Background rates; Expected rates; Adverse events; COVID-19; Vaccination; Vaccine safety; Vaccine surveillance; Vaccine benefit-risk assessment

INTRODUCTION

As of August 2021, three vaccines are being used in the United States to prevent severe COVID-19 (1). Since emergency use authorization of these vaccines, large-scale COVID-19 vaccination programs have been implemented in the United States. Given the unprecedented speed of COVID-19 vaccine development, the use of novel vaccine technologies, and rapid large-scale national COVID-19 vaccination, it is reasonable that people may have concerns about vaccine safety (2).

Mild to moderate local or systematic reactions after COVID-19 vaccination are common; reports of anaphylaxis and other serious adverse events such as myocarditis, thrombosis with thrombocytopenia syndrome (TTS), or Guillain-Barré syndrome (GBS) have been rare (3). Although a close temporal association between vaccination and an adverse event does not establish that the vaccine caused the event, such temporally associated events may lead to greater concern than more remote events. Public concern about vaccine safety can contribute to vaccine hesitancy, result in vaccine misinformation, and adversely affect vaccine uptake (4). The U.S. COVID-19 vaccine safety program comprehensively monitors the safety of all authorized COVID-19 vaccines to assess if potential adverse events are vaccine-related and exceed the expected background rate (i.e., incidence rate observed in a given population in the absence of vaccination). This monitoring is vital to ensuring safe vaccines and to promote vaccine confidence among the public.

Knowledge of the expected rates of medical conditions that would occur coincidentally (i.e., as a result of background incidence) in the U.S. population aids COVID-19 vaccine safety surveillance efforts by providing a baseline to determine if observed rates of adverse events following vaccination exceed expected rates regardless of vaccination. This information can also guide COVID-19 vaccine safety communication to the public and inform benefit-risk analyses of COVID-19 vaccines. We calculated background rates and estimated expected rates of 21 medical conditions considered potential adverse events of special interest (AESI) following COVID-19 vaccination and calculated the expected rates of each AESI that would coincidentally occur among vaccinated

persons in the general population within 1 day, 7 days, and 42 days after vaccination due to chance alone.

METHODS

Manuscript selection and eligibility criteria for AESI

For this analysis, we used a list of medical conditions considered potential AESI following COVID-19 vaccination from Gubernot et al. (5) (Supplemental Table 1). This list was compiled by vaccine safety experts from the Centers for Disease Control and Prevention (CDC) and FDA; medical conditions considered as AESI were selected based on general or historical vaccine safety monitoring outcomes and theoretical concerns related to COVID-19 disease outcomes

We reviewed the articles considered by Gubernot et al. (5). We restricted eligible studies for this analysis to those that were published in English, described a systematic process for case identification, used established and widely accepted case definitions, and included cases identified from a well-enumerated U.S. population, and reported a denominator (person-years) and numerator (number of events). If the denominator was not available in the article, we used the reported incidence rate and numerator to estimate a denominator. We excluded published articles that focused only on specific sub-populations (e.g. based on age, sex, and ethnicity), reported incidence rates from a non-U.S. population, were published prior to 1970, or where the denominator and numerator were missing.

General population rates and rates by age group and sex for all-cause mortality, and mortality attributed to heart disease and cerebrovascular disease were obtained from the National Vital Statistics System (NVSS) (6). We obtained sudden cardiac death rates from the American Heart Association's Heart Diseases and Stroke Statistics 2020 update report (7).

Analysis

We used meta-analytic methods to estimate pooled rates of potential AESI using incidence rates obtained from eligible incidence studies for each medical condition considered as an AESI after

COVID-19 vaccination. We used the 'metarate' function in R package meta v. 4.15-1 to conduct a random effects model to estimate a pooled incidence rate and 95% confidence interval (95% CI) for each AESI. The pooled incidence rate and 95% CI was used as the background rate for each AESI. For medical conditions where only one article met the eligibility criteria, we used the reported incidence rate and 95% CI as the background rate. Because we obtained rates for all mortality events from one source, we used the reported mortality rate for each mortality event as the background rate.

Calculating expected AESI rates

Using the derived background rates, we calculated the number of expected AESI that would occur coincidentally (i.e., not vaccine-related but as a result of background incidence) in 10,000,000 vaccinated people in the general U.S. population within 1 day, 7 days, and 42 days after vaccination with a COVID-19 vaccine. These post-vaccination time intervals were selected because the initial symptoms of an AESI commonly occur within hours and up to 42 days after vaccination, although they could occur later as well. To calculate the number of expected coincident AESI we divided the background rate by 365.25 to obtain a daily rate and by 100,000 to obtain a daily incidence rate per person. Then, we calculated the product of the daily incidence rate per person for each AESI, the number of vaccinated people (10,000,000), and the associated post-vaccination time interval (1 day, 7 days, or 42 days). For example, an AESI with a background rate of 1.87/100,000 person-years would yield a daily incidence rate per person of 0.0000000512. The product of the daily incident AESI rate per person (0.0000000512), the number of vaccinated people (10,000,000), and the post-vaccination time interval (7 days in this case) is 3.58. Thus, we would expect to observe 3.6 cases of the AESI to occur coincidentally in 10,000,000 vaccinated people in the general population within 7 days of receiving a COVID-19 vaccine, assuming a background rate of 1.87/100,000 person-years. This analysis was exempt from Institutional Review Board review as it did not involve collection of original data from human subjects.

RESULTS

We summarize the background rates and estimated expected rates for Guillain-Barre Syndrome, myopericarditis, all-cause deaths and deaths caused by diseases of the heart, cerebrovascular diseases, and sudden cardiac events below and in Table 1. The background rates and expected rates for the remaining 14 AESI are summarized in the supplemental file and supplemental Table 2.

Guillain-Barre Syndrome

We estimated a background rate of 2.0/100,000 person-years after a meta-analysis of six incidence studies of Guillain-Barre syndrome (8-13). Based on this background rate, we estimated that we would expect 0.5 coincident cases in 10,000,000 vaccinated persons within 1 day of vaccination; 3.7 coincident cases in 10,000,000 vaccinated persons within 7 days of vaccination; and 22.4 coincident cases in 10,000,000 vaccinated persons within 42 days of vaccination.

Myopericarditis

We used the incidence rate from one study (14) as the background rate for myopericarditis (1.3/100,000 person-years). At this background rate, we would expect to observe 0.3 coincident cases in 10,000,000 vaccinated persons within 1 day post-vaccination; 2.4 coincident cases in 10,000,000 vaccinated persons within 7 days post-vaccination; and 14.3 coincident cases in 10,000,000 vaccinated persons within 42 days post-vaccination.

All-cause deaths

We used all-cause mortality rate from NVSS (6) as the background rate for all-cause deaths (863.8/100,000 persons). We estimated that we would expect 236.5 coincident all-cause deaths in 10,000,000 vaccinated people within 1 day of vaccination; 1,655.5 coincident all-cause deaths in 10,000,000 vaccinated people within 7 days of vaccination; and 9,932.8 coincident all-cause deaths in 10,000,000 vaccinated people within 42 days of vaccination. The expected rates increased progressively by age and was consistently higher in males than females.

Deaths attributed to heart disease

Using heart disease mortality rate from (6) as the background rate for deaths attributed to heart disease (198.8/100,000 persons) , we estimated that we would expect 54.4 coincident deaths attributed to heart disease among 10,000,000 vaccinated people within 1 day of vaccination; 381.0 coincident deaths attributed to heart disease among 10,000,000 vaccinated people within 7 days of vaccination; and 2,286.0 coincident deaths attributed to heart disease among 10,000,000 vaccinated people within 42 days of vaccination. The expected rates increased progressively by age and was consistently higher in males than females.

Deaths attributed to cerebrovascular disease

Using cerebrovascular disease mortality rate (6) as the background rate for deaths attributed to cerebrovascular disease (44.9/100,000 persons) , we estimated that we would expect 12.3 coincident cerebrovascular disease deaths among 10,000,000 vaccinated people within 1 day of vaccination; 86.1 coincident cerebrovascular deaths among 10,000,000 vaccinated people within 7 days of vaccination; and 516.3 coincident cerebrovascular deaths among 10,000,000 vaccinated people within 42 days of vaccination. The expected rates increased progressively by age and was higher in females than males.

Sudden cardiac deaths

We used the mortality rate attributed to sudden cardiac events (97.1/100,000 persons) (7) as the background rate. Based on this background rate, we estimated that we would observe 26.6 coincident sudden cardiac deaths in 10,000,000 vaccinated people within 1 day of vaccination; 186.1 sudden cardiac deaths in 10,000,000 vaccinated people within 7 days of vaccination; and 1,116.6 coincident sudden cardiac deaths in 10,000,000 vaccinated people within 42 days of vaccination. The expected rates increased progressively by age and was consistently higher in males than females.

DISCUSSION

We estimated rates of select medical conditions considered potential AESI expected to occur among vaccinated persons in the general U.S. population within 1 day, 7 days, and 42 days

after COVID-19 vaccination. Observed rates of these medical conditions following vaccination can be compared to the rates that would be expected to occur coincidentally among vaccinated persons in the general population regardless of COVID-19 vaccination. This comparison can help distinguish potential vaccine-related AESI from coincidental occurrences in vaccinated persons (4), is important for post-authorization safety monitoring of COVID-19 vaccines, and complements clinical investigations by the U.S. CDC and FDA to understand the etiology of reports of potential AESI in vaccinated persons.

Expected rates of these medical outcomes in the general population can also inform public health safety communication about the COVID-19 vaccine (4, 5). Spurious associations between vaccination and adverse health events can undermine vaccine acceptance and uptake and present challenges to achieving community immunity that is necessary for population-level protection (4). Communicating COVID-19 vaccine safety information to the public that explains that the observed rate of potential AESI in the vaccinated population is not greater than what would be expected in the absence of vaccination may help the public better understand that these events are coincident occurrences, that are temporally but not causally associated with vaccination (4). Framing vaccine safety communication this way may assuage vaccine safety concerns. Knowledge of expected rates of a potential AESI can also be useful in benefit-risk assessments of specific COVID-19 vaccines (15).

There are limitations to this analysis. We only calculated expected rates for a limited set of medical conditions considered as potential AESI based on the list developed by Gubernot and colleagues (5). This list does not represent the full spectrum of potential vaccine safety outcomes of concern. Generalizability of the expected rates of some AESI to subpopulations (e.g., age, sex, and race/ethnicity) is limited because we lacked incidence rate by subpopulations. Changes in healthcare utilization during the COVID-19 pandemic may affect the background rates of some AESI and thus, the expected rates, limiting the generalizability of these findings. We calculated expected rates of potential AESI based on background rates obtained from incidence studies, consequently, there may be residual or confounding biases in the studies that we could not adequately control. The expected

rates of AESI presented here are based on U.S. studies and likely are not applicable to most non-U.S. populations. At the time of this analysis, there were no published papers available that report U.S. incidence estimates for TTS and myocarditis, AESI that have been associated with COVID-19 vaccination. We were therefore unable to calculate their background or expected rates.

In conclusion, knowledge of expected rates of potential AESI in vaccinated persons in the general population is vital to COVID-19 vaccine safety monitoring, distinguishing vaccine-related events from coincident events that are temporally associated with but unrelated to vaccination, informing public health COVID-19 vaccine safety communication, promoting public confidence in the vaccine, and conducting specific COVID-19 vaccine benefit-risk assessments.

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Table 1. Background rates and expected rates for select adverse events of special interest (number of cases/10,000,000 vaccinated people) and mortality events (number of deaths/10,000,000 vaccinated persons)

Adverse events of special interest			Estimated background rate (cases/100,000 person-years) and 95% confidence interval	Expected rates within 1 day of vaccination (cases/10,000,000 vaccinated persons) and (95% confidence interval)	Expected rates within 7 days of vaccination (cases/10,000,000 vaccinated persons) and (95% confidence interval)	Expected rates within 42 days of vaccination (cases/10,000,000 vaccinated persons) and (95% confidence interval)
Medical conditions						
Guillain-Barre syndrome			2.0 (1.4-2.6)	0.5 (0.4-0.7)	3.7 (2.6-4.9)	22.4 (15.5-29.4)
Pericarditis			7.6 (3.7-11.4)	2.1 (1.0-3.1)	14.6 (7.0-21.9)	86.8 (42.2-131.4)
Myopericarditis			1.3 (0.4-2.1)	0.3 (0.1-0.6)	2.4 (0.8-4.0)	14.3 (5.0-23.7)
Mortality event	**Sex**	**Age group (years)**	**Background rate (deaths/100,000 persons)**	**Expected rates within 1 day of vaccination (deaths/10,000,000 vaccinated persons)**	**Expected rates within 7 days of vaccination (deaths/10,000,000 vaccinated persons)**	**Expected rates within 42 days of vaccination (deaths/10,000,000 vaccinated persons)**
All-cause deaths	All	1–4	24.3	6.7	12.8	279.4
		5–14	13.6	3.7	26.1	156.4
		15–24	74.0	20.3	141.8	850.9
		25–34	132.8	36.4	254.5	1527.1
		35–44	195.2	53.4	374.1	2244.6
		45–54	401.5	109.9	769.5	4616.8
		55–64	885.8	242.5	1697.6	10185.8
		65–74	1790.9	490.3	3432.3	20593.5
		75–84	4472.6	1224.5	8571.7	51430.3
		≥85	13573.6	3716.3	26013.7	156082.5
		Total	**863.8**	**236.5**	**1655.5**	**9932.8**
	Male	1–4	27.3	7.5	52.3	313.9
		5–14	15.6	4.3	29.9	179.4
		15–24	106.1	29.1	203.3	1220.0
		25–34	183.3	50.2	351.3	2107.8
		35–44	249.4	68.3	477.9	2867.8
		45–54	496.5	135.9	951.5	5709.2
		55–64	1112.3	304.5	2131.7	12790.3
		65–74	2190.2	599.6	4197.5	25185.1
		75–84	5254.0	1438.5	10069.3	60415.6
		≥85	14689.2	4021.7	28151.8	168910.7
		Total	**897.2**	**245.6**	**1719.5**	**10316.9**
		1–4	21.1	5.8	40.4	242.6

	Female	5–14	11.4	3.1	21.9	131.1
		15–24	40.4	11.1	77.4	464.6
		25–34	80.8	22.1	154.9	929.1
		35–44	141.4	38.7	271.0	1626.0
		45–54	309.0	84.6	592.2	3553.2
		55–64	674.7	184.7	1293.1	7758.4
		65–74	1440.4	394.4	2760.5	16563.1
		75–84	3869.1	1059.3	7415.1	44490.7
		≥85	12966.5	3550.0	24850.2	149101.4
		Total	**831.4**	**227.6**	**1593.4**	**9560.3**
Deaths caused by diseases of the heart (ICD10 codes I00–I09, I11, I13, I20–I51)	All	1–4	0.8	0.2	1.5	9.2
		5–14	0.4	0.1	0.8	4.6
		15–24	2.1	0.6	4.0	24.2
		25–34	8.1	2.2	15.5	93.1
		35–44	25.4	7.0	48.7	292.1
		45–54	77.1	21.1	147.8	886.6
		55–64	190.7	52.2	365.5	2192.9
		65–74	392.9	107.6	753.0	4517.9
		75–84	1028.4	281.6	1970.9	11825.5
		≥85	3882.9	1063.1	7441.6	44649.4
		Total	**198.8**	**54.4**	**381.0**	**2286.0**
	Male	1–4	0.8	0.2	1.5	9.2
		5–14	0.5	0.2	0.9	5.8
		15–24	2.8	0.8	5.4	32.20
		25–34	10.7	2.9	20.5	123.0
		35–44	34.7	9.5	66.5	399.0
		45–54	109.1	29.9	209.1	1254.5
		55–64	273.2	74.8	523.6	3141.5
		65–74	538.5	147.4	1032.0	6192.2
		75–84	1306.8	357.8	2504.5	15026.9
		≥85	4421.1	1210.4	8473.0	50838.1
		Total	**216.9**	**59.4**	**415.7**	**2494.1**
	Female	1–4	0.8	0.2	1.5	9.2
		5–14	0.4	0.1	0.8	4.6
		15–24	1.4	0.4	2.7	16.1
		25–34	5.5	1.5	10.5	63.2
		35–44	16.2	4.4	31.1	186.3
		45–54	45.9	12.6	88.0	527.8
		55–64	113.9	31.2	218.3	1309.7

		65–74	265.1	72.6	508.1	3048.4
		75–84	813.5	222.7	1559.1	9354.4
		≥85	3589.9	982.9	6880.0	41280.2
		Total	**181.2**	**49.6**	**347.3**	**2083.6**
Deaths caused by cerebrovascular diseases (ICD10 codes I60–I69)	All	1–4	0.4	0.1	0.8	4.6
		5–14	0.2	0.1	0.4	2.3
		15–24	0.4	0.1	0.8	4.6
		25–34	1.3	0.4	2.5	15.0
		35–44	4.4	1.2	8.4	50.6
		45–54	12.3	3.4	23.6	141.4
		55–64	30.3	8.3	58.1	348.4
		65–74	76.4	20.9	146.4	878.5
		75–84	263.1	72.0	504.2	3025.3
		≥85	993.5	272.0	1904.1	11424.2
		Total	**44.9**	**12.3**	**86.1**	**516.3**
Deaths caused by cerebrovascular diseases (ICD10 codes I60–I69)	Male	1–4	0.5	0.2	1.0	5.8
		5–14	0.3	0.1	0.6	3.5
		15–24	0.4	0.1	0.8	4.6
		25–34	1.5	0.4	2.9	17.3
		35–44	5.1	1.4	9.8	58.6
		45–54	14.4	3.9	27.6	165.6
		55–64	36.2	9.9	69.4	416.3
		65–74	86.7	23.7	166.2	997.0
		75–84	273.5	74.9	524.2	3145.0
		≥85	883.3	241.8	1692.8	10157.1
		Total	**38.4**	**10.5**	**73.6**	**441.6**
	Female	1–4	0.3	0.1	0.6	3.5
		5–14	0.2	0.1	0.4	2.3
		15–24	0.3	0.1	0.6	3.5
		25–34	1.1	0.3	2.1	12.7
		35–44	3.8	1.0	7.3	43.7
		45–54	10.2	2.8	19.6	117.3
		55–64	24.7	6.8	47.3	284.0
		65–74	67.4	18.5	129.2	775.0
		75–84	255.1	69.8	488.9	2933.4
		≥85	1053.4	288.4	2018.8	12113.0
		Total	**51.3**	**14.1**	**98.7**	**592.2**
		<1	11.2	3.1	21.5	128.8
		1–4	2.2	0.6	4.2	25.3

Sudden cardiac death[1]	All	5–9	1.2	0.3	2.3	13.8
		10–14	1.2	0.3	2.3	13.8
		15–19	2	0.6	3.8	23.0
		20–24	3.2	0.9	6.1	36.8
		25–29	5.4	1.6	10.4	62.1
		30–34	8	2.2	15.3	92.0
		35–39	13.3	3.6	25.6	152.9
		40–44	20.9	5.7	40.1	240.3
		45–49	35.6	9.8	68.2	409.4
		50–54	64.8	17.7	124.2	745.1
		55–59	102.3	28.0	196.1	1176.4
		60–64	154.4	42.3	295.9	1775.4
		65–69	220.6	60.4	422.8	2536.7
		70–74	327.8	89.8	628.2	3769.4
		75–79	512.4	140.3	982.0	5892.1
		80–84	823.4	225.4	1578.0	9468.3
		Total	**97.1**	**26.6**	**186.1**	**1116.6**

[1] mentioned in death certificate as contributory to death