DARE-SAFE: Denominator-Adjusted Rate Estimates of Substance Adverse Events Frequency Evaluation in Pharmaceuticals and Vaccines

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Article

DARE-SAFE: Denominator-Adjusted Rate Estimates of Substance Adverse Events Frequency Evaluation in Pharmaceuticals and Vaccines

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Abstract: Objective: This study introduces the Denominator-Adjusted Rate Estimates of Substance Adverse Events Frequency Evaluation (DARE-SAFE) method to analyze pharmacovigilance reporting rates for vaccines and common pharmaceuticals. Methods: We calculated reporting rates for the top 250 most prescribed drugs in the US FDA Adverse Event Reporting System (FAERS) and common vaccines in the Vaccine Adverse Events Reporting System (VAERS). For vaccines, we used CDC dose data and OpenVAERS reports. For pharmaceuticals, we utilized prescription data from ClinCalc and FAERS reports for 2022. Results: VAERS reporting rates varied significantly across vaccine types. COVID-19 vaccines showed a 63.0±0.6 times higher rate of VAERS deaths per dose and an 18.95±0.02 times higher rate of total adverse event reports compared to influenza vaccines. The ratio of total VAERS reports to deaths for vaccines was approximately 70:1 (R^2=0.966). For pharmaceuticals, the ratio of total adverse event reports to deaths was about 43:1 (R^2=0.697), with a strong correlation between serious adverse events and deaths (ratio 11:1, R^2=0.768). Conclusion: DARE-SAFE provides a standardized method for comparing reporting rates across different medical products. The observed differences between vaccines and pharmaceuticals, as well as among different vaccine types, warrant further investigation into reporting practices, actual safety profiles, and potential biases in surveillance systems.

Keywords: Pharmacovigilance; Vaccine Adverse Event; Drug Safety; Vaccine Adverse Event Reporting System

Introduction

Post-marketing surveillance utilizing passive reporting carries the caveat that lacking knowledge on the number of people administered a drug, raw numbers of reports do not reflect actual safety risk. This analysis calculates the reporting rates for the top 250 most prescribed drugs in the US FDA Adverse Event Reporting System, as well as common vaccines in the Vaccine Adverse Events Reporting System. While reporting rates and incidence rates are two different quantities, this data may be valuable as a resource in pharmacovigilance to identify changing trends in reported drug and vaccine adverse events (AEs), while remaining agnostic to the source of the trend, be it in reporting behaviour or actual risk.

The use of pharmacovigilance systems has come with caveats to the use of said systems, that one is unable to assign causality or to determine rates of adverse events from reporting frequencies. The use of any dataset comes with caveats, and VAERS is no different, requiring care in analysis and reporting. While we cannot calculate incidence rates from VAERS reports, it is possible to calculate the reporting rates, given a suitable denominator (number of doses). We make this clarification at the outset. Adverse events are typically underreported, where more serious and temporally associated

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events are more likely to be reported, and minor events with a less salient association with vaccination tend to be more underreported (less likely to be reported) (1).

The Problem of Inferring Rates in the Vaccine Adverse Event Reporting System

Pharmaceutical drugs are commonly understood to have side effects associated with them. These side effects are measured against their benefits to determine if it is in the patient's best interest to take a prescription for a drug. By comparison, vaccines are understood to have side effects, ranging from site pain and cold and flu symptoms to severe impairments and death, yet outside of special cases of allergy to a component, are almost unanimously determined by medical professionals to be in the patient's best interest.

This promotion by medical professional belies significant financial incentives for physicians to promote vaccines, which includes bonuses up to tens of thousands of dollars (2,3).

While vaccines can lower the incidence and severity of infectious diseases, they may not be appropriate in every case. For a proper comparison of utility with downsides, it is important to quantify levels of risk to compare with benefits. Promotion of vaccines is often laden with absolute statements. For example, official messaging on Covid-19 vaccines often included the words "Safe and effective", without reference to what these meant quantitatively. Without a quantitative measure, "safe" communicates to the audience that the product is without risk, and "effective" communicates that the vaccine prevents the disease that the vaccine is targeted against. For the case of Covid-19 and all vaccines, neither is absolutely true.

It is commonly said that VAERS cannot be used to infer adverse event rates. While this is technically true, it can provide a helpful estimation. If the number of doses is known, than it is possible to provide the reporting rate per a constant number of doses. This should be considered only a proxy measurement for risk, and not an absolute measure, as it does not account for the reporting rate, which may differ between vaccines due to increased salience of pharmacovigilance reporting.

Many factors influence the reporting rate of VAERS reports, though it is widely accepted to be underreported, with reporting rates differing by condition, severity, and salience of the connection with vaccination. While caveats need to be accounted for, this does not mean that VAERS reports per dose is a useless measure, as is often implied. It may be informative of the relative safety of vaccines, and should importantly be corroborated with active surveillance tools. In principle, researchers are allowed to access active surveillance data; but in practice, requests can be declined by the agencies acting as custodians for the data.

Some AE rates for vaccines are reported, though our literature search has not revealed data on VAERS reports per dose for major vaccines as a resource. We include this data as a means of comparison of relative reporting rates between vaccines. Two analyses have compared reporting rates of Covid-19 vaccines with Influenza (4,5). We expand this analysis to more vaccines in the CDC schedule.

If there is a large difference in VAERS reporting rates per dose between vaccines which does not correspond with an actual increased risk of adverse events for a given vaccine, it becomes informative to study the factors resulting in the discrepancy. As vaccine adverse event underreporting is a significant challenge, studying the factors behind greater reporting (as long as reports are truthful) can help pharmacovigilance efforts for current and future vaccines. In the case where differential reporting rates correspond to discrepancies in actual risk, it is important to study the factors driving the increased risk, as this may improve the safety of the vaccination program as a whole.

Pharmacovigilance Reporting for Pharmaceutical Drugs

It is less controversial that pharmaceutical drugs have side effects and potential adverse events associated with them. However, awareness of pharmacovigilance programs are limited, and adverse events are underreported for drugs as well as vaccines (6). In the below analysis, we report the crude rates of drug associated adverse events per prescriptions. We wish to emphasize that the dataset for

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VAERS reporting rates is different from the dataset we provide for pharmaceutical adverse event reporting rates, and we provide these by prescription, instead of per dose, as is the case for vaccine adverse events, i.e. the rates are not directly comparable.

Methods

VAERS Reporting Rates by Vaccine Type

Using numbers of doses in CDC data, we search the number of VAERS reports for a given vaccine type using the resource OpenVAERS.com, which aggregates reports and provides the numbers of reports for given search terms. Additional filters can filter for deaths. We report both the total number of reports, as well as the deaths for a given vaccine type for the time period specified by the CDC data, ranging from Jan.1, 2022 to Dec.31, 2022, available at https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/vaccines/vicp-stats-01-01-25.pdf, accessed 9 January, 2025.

VAERS Reporting Rate by COVID-19 Vaccine Manufacturer

We delineate the VAERS reporting rates by Covid-19 vaccine manufacturer, using numbers of doses (Up to December 31, 2022) from https://ourworldindata.org/grapher/covid-vaccine-doses-by-manufacturer?country=~USA, and VAERS reports using the OpenVAERS search by vaccine manufacturer, for reports up to and including 2022.

FAERS Reporting Rates by Drug

Data on the number of prescriptions for a given drug per year are obtained through the website https://clincalc.com. The number of FAERS reports for the year 2022 is found for that same year using the FDA database, available at https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. FAERS reports are also delineated by serious adverse events and deaths. Prescription rates for the year 2022 are obtained from https://clincalc.com/DrugStats/Drugs.

Results

VAERS Reporting Rates by Vaccine Type

Calculating the VAERS reporting rate per dose produces significant variation in the reporting rates for AEs across vaccine type. Given the possible variation in AE rates, especially for common and non serious events like site pain and cold/flu symptoms, we examine deaths, finding significant variation per dose as well, with Covid-19 vaccines being considerably more dangerous than other commonly administered vaccines, such as influenza.

Since influenza is one of the relatively safer vaccines with a large number of doses distributed, we express VAERS reporting rates as multiples of influenza, and do the same for VAERS deaths. For Covid-19 vaccines, we observe a 63.0±0.6 times higher rate of VAERS deaths per dose than influenza. For total AEs, Covid-19 vaccines have a rate of VAERS reports 18.95±0.02 times the influenza rate. These findings suggest differences in vaccine safety and/or reporting practices between the two vaccines.

Using a fixed intercept model, and weighting by the number of VAERS reports, the ratio of total reports to deaths is 70 (R^2=0.966).

Table 1. VAERS reporting rates per doses administered for vaccines in VAERS.

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Vaccine Name	Number of Doses Distributed (2006-2022)	Number of VAERs reports	VAERS reporting rate per dose	VAERS deaths	VAERS deaths reporting rate
DT	794,777	462	0.000581	2	2.51643E-06
DTaP	122,237,653	25629	0.00021	656	5.3666E-06
DTaP-Hep B-IPV	94,331,585	9990	0.000106	419	4.44178E-06
DTaP-HiB	1,135,474	380	0.000335	1	8.80689E-07
DTaP-IPV	40,456,384	9818	0.000243	8	1.97744E-07
DTaP-IPV-HiB	89,568,786	8906	9.94E-05	224	2.50087E-06
DTaP-IPV-HiB-Hep B	2,021,770	526	0.00026	3	1.48385E-06
DTP	0	556	N/A	3	N/A
DTP-HiB	0	57	N/A	2	N/A
Hep A+Hep B	19,811,507	2893	0.000146	8	4.03806E-07
Hep B-HiB	4,787,457	1000	0.000209	18	3.75982E-06
Hepatitis A (Hep A)	231,034,565	30930	0.000134	85	3.6791E-07
Hepatitis B (Hep B)	248,816,802	19737	7.93E-05	222	8.92223E-07
HiB	159,451,493	21526	0.000135	435	2.7281E-06
HPV	158,878,541	42464	0.000267	109	6.86059E-07
Influenza	2,407,000,000	149512	6.21E-05	650	2.70046E-07
IPV	85,815,525	16104	0.000188	93	1.08372E-06
Measles	135,660	118	0.00087	2	1.47427E-05
Meningococcal	152,565,553	31050	0.000204	54	3.53946E-07
MMR	134424338	35743	0.000266	88	6.54643E-07
MMR-Varicella	42936444	15668	0.000365	20	4.65805E-07
Mumps	110749	65	0.000587	0	0
OPV	0	188	N/A	5	N/A
Pneumococcal	517159908	83537	0.000162	810	1.56625E-06
Rotavirus	150866652	19899	0.000132	476	3.1551E-06
Rubella	422548	98	0.000232	0	0
Td	79443263	3322	4.18E-05	9	1.13288E-07
Tdap	358134237	39153	0.000109	59	1.64743E-07
Tetanus	3838993	1226	0.000319	4	1.04194E-06
Varicella	143906028	48863	0.00034	84	5.83714E-07
Covid-19	663000000 (7)	781075	0.001177	11288	1.70154E-05

Table 2 includes the analysis for Covid-19 by vaccine manufacturer, showing higher levels per dose for Johnson&Johnson, with comparable levels of risk when taking into account that Pfizer/BioNTech and Moderna vaccines are a two dose series compared to one dose for Johnson&Johnson.

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VAERS Reporting Rates by COVID-19 Vaccine Manufacturer

Table 2. VAERS reporting rates per doses administered for Covid-19 vaccines in VAERS.

Covid-19 Vaccine Manufacturer	Doses (cumulative to 2022-12-31 in USA)	Number of VAERS reports	Number of VAERS death reports	VAERS reporting rate per dose	VAERS death reporting rate per dose
Pfizer/BioNTech	395801679	398,648	6530	0.001007	1.64982E-05
Moderna	248752253	371,774	6056	0.001495	2.43455E-05
Johnson&Johnson	18953653	61,262	1093	0.003232	5.7667E-05
Novavax	69623	627	0	0.009006	0

Using a fixed intercept model, and weighting by the number of VAERS reports, the ratio of total reports to deaths is 59 ($R^2 = 0.989$).

FAERS Reporting Rates for 250 Most Prescribed Pharmaceuticals in 2022

For the sake of brevity, we have included only the top 10 most prescribed medications in 2022 in Table 3. The full dataset is available in Supplementary Table 1.

Table 3. FAERS reporting rates per prescription and patient for the top 10 most prescribed drugs in USA in 2022.

Drug Name	Total Prescri-ptions (2022, Millions)	Total Patients (2022, Millions)	Total AEs	Serious AEs	Deaths	AEs per prescription	Serious AEs per prescription	Deaths per prescription	AEs per patient	Serious Aes per patient	Deaths per patient
Atorvastatin	109.583	27.936	3834	3601	305	3.4987E-05	3.2861E-05	2.7833E-06	0.00013724	0.0001289	1.0918E-05
Metformin	86.748	19.536	5164	4631	663	5.9529E-05	5.3385E-05	7.6428E-06	0.00026433	0.00023705	3.3937E-05
Lisinopril	82.514	20.314	2564	1387	286	3.1074E-05	1.6809E-05	3.4661E-06	0.00012622	6.8277E-05	1.4079E-05
Levothyroxine	82.432	18.130	1756	1370	252	2.1302E-05	1.662E-05	3.0571E-06	9.6854E-05	7.5564E-05	1.3899E-05
Amlodipine	70.766	17.790	3903	3682	726	5.5153E-05	5.203E-05	1.0259E-05	0.00021940	0.00020697	4.081E-05
Metoprolol	65.245	15.543	2360	2096	400	3.6171E-05	3.2125E-05	6.1307E-06	0.00015184	0.00013485	2.5735E-05
Albuterol	59.075	19.265	2305	2073	109	3.9018E-05	3.5091E-05	1.8451E-06	0.00011964	0.00010076	5.6578E-06

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Losartan	53.556	13.150	1194	980	157	2.2295E-05	1.8299E-05	2.9315E-06	9.0798E-05	7.4525E-05	1.1939E-05
Omeprazole	52.133	13.802	4844	4405	536	9.2916E-05	8.4496E-05	1.0281E-05	0.00035096	0.00031915	3.8835E-05
Gabapentin	40.141	9.890	5263	4149	1195	0.00013111	0.00010336	2.977E-05	0.00053218	0.00041953	0.00012083

For the sake of brevity, we have included only the top 10 most prescribed medications in 2022 in Table 3. The full dataset is available in Supplementary Table 1.

We observe a strong correlation between the reporting rates of serious adverse events and the reporting rates for deaths. Using a fixed intercept model, and weighting by the number of adverse event reports, the ratio of adverse event reports to deaths is 43±2 (R^2=0.697).

Using a fixed intercept model, and weighting by the number of serious adverse event reports, the ratio of serious adverse event reports to deaths is 11.217 ± 0.002 (R^2=0.768).

Discussion

This work presents Denominator-Adjusted Rate Estimates of Substance Adverse Events Frequency Evaluation (DARE-SAFE) for pharmaceuticals and vaccines, which provides values for the pharmacovigilance reporting rates for vaccines and common pharmaceuticals. The DARE-SAFE analysis provides a comprehensive examination of adverse event reporting rates for both vaccines and pharmaceuticals, offering valuable insights into pharmacovigilance data. This study calculates reporting rates for the top 250 most prescribed drugs in the US FDA Adverse Event Reporting System and common vaccines in the Vaccine Adverse Events Reporting System (VAERS).

A key finding of the analysis is the significant variation in VAERS reporting rates across different vaccine types. Notably, COVID-19 vaccines showed considerably higher reporting rates compared to other commonly administered vaccines, such as influenza. The study found that COVID-19 vaccines had a 63.0±0.6 times higher rate of VAERS deaths per dose than influenza vaccines, and an 18.95±0.02 times higher rate of total adverse event reports.

The analysis also revealed a consistent ratio of approximately 70:1 for total VAERS reports to deaths for vaccines. This ratio was determined using a fixed intercept model weighted by the number of VAERS reports, with an R^2 value of 0.966, indicating a strong correlation.

For pharmaceuticals, the study examined the FDA Adverse Event Reporting System (FAERS) data for the year 2022. The analysis found a lower ratio of about 43:1 for total adverse event reports to deaths, compared to the 70:1 ratio observed in vaccines. Additionally, a strong correlation was observed between serious adverse events and deaths in pharmaceutical reporting, with a ratio of approximately 11:1.

These findings underscore the importance of context when interpreting pharmacovigilance data. While DARE-SAFE provides a standardized method for comparing reporting rates, it's crucial to remember that these rates do not directly equate to incidence or causality. The observed differences between vaccines and pharmaceuticals, as well as among different vaccine types, warrant further investigation into reporting practices, actual safety profiles, and potential biases in surveillance systems.

References

1. García-Abeijon P, Costa C, Taracido M, Herdeiro MT, Torre C, Figueiras A. Factors Associated with Underreporting of Adverse Drug Reactions by Health Care Professionals: A Systematic Review Update. Drug Saf. 2023;46(7):625–36.

2. Staff N. Strategies to Increase COVID-19 Vaccination Rates in Medicaid Enrollees: Considerations for State Leaders [Internet]. NASHP. 2021 [cited 2025 Jan 23]. Available from:

https://nashp.org/strategies-to-increase-covid-19-vaccination-rates-in-medicaid-enrollees-considerations-for-state-leaders-report/

3. Medi-Cal COVID-19 Vaccine Incentive Program Evaluation Report August 29, 2021 – March 6, 2022 [Internet]. California Department of Health Care Services; 2024 Feb [cited 2025 Jan 23]. Available from: https://www.dhcs.ca.gov/Documents/Covid-Vaccine-Incentive-Evaluation-Report.pdf

4. Rose J. A report on the US Vaccine Adverse Events Reporting System (VAERS) of the COVID-19 messenger ribonucleic acid (mRNA) biologicals. Science, Public Health Policy, and the Law. 2021 May;2:59-80.

5.Kim MS, Jung SY, Ahn JG, Park SJ, Shoenfeld Y, Kronbichler A, Koyanagi A, Dragioti E, Tizaoui K, Hong SH, Jacob L. Comparative safety of mRNA COVID-19 vaccines to influenza vaccines: A pharmacovigilance analysis using WHO international database. Journal of Medical Virology. 2022 Mar;94(3):1085-95.

6. Putri RA, Ikawati Z, Rahmawati F, Yasin NM. An Awareness of Pharmacovigilance Among Healthcare Professionals Due to an Underreporting of Adverse Drug Reactions Issue: A Systematic Review of the Current State, Obstacles, and Strategy. Curr Drug Saf. 2024;19(3):317–31.

7. Our World in Data [Internet]. [cited 2025 Jan 13]. Total COVID-19 vaccine doses administered. Available from: https://ourworldindata.org/grapher/cumulative-covid-vaccinations?country=~USA