MEMO

DATE: August 1, 2024

TO: Wayne Salter, Executive Director NDHHS

FROM: District 31 Representative Karen M. Rohr (PhD Nursing & Board Certified Nurse Practitioner)

RE: Vaccine Safety Surveillance/Proposal for Vaccine Safety Data Transparency Legislation

1. Synopsis

The goal of this initiative is to lay the groundwork for vaccine safety data transparency legislation to be introduced in the next session. A methodology for vaccine safety surveillance is proposed and will involve a retrospective cohort analysis of death and vaccination records. The contemplated legislation will require HHS to maintain a death and vaccination database for all vaccines given in this state and make that database available online for public use. The legislation will also mandate the publication of retrospective cohort analysis for each vaccine on a regular schedule. As a pilot project, HHS should conduct such an analysis of COVID vaccines to better inform and guide the drafting of this legislation.

2. Background

Fueled by concerns over the safety of COVID vaccines, SB 2384 was introduced during the last legislative session. Originally drafted to ban mRNA vaccines, the bill was later amended to simply provide for a legislative management study. After its second reading, the bill failed to pass.

The Bismarck Tribune, in its 4/12/23 editorial, cheered this outcome:

> The House did the state a favor last week when it rejected Senate Bill 2384 that was for an optional 2023-24 interim legislative study of "the long-term health effects on human beings of vaccines." There have been numerous federal and private studies of vaccines and there will be more. The Legislature isn't equipped to do a deep dive into vaccines.

While the Legislature isn't equipped to "do a deep dive" into vaccine safety, North Dakota Health and Human Services certainly is. In fact, it is one of the department's vital functions.

3. HHS and Vaccine Safety Surveillance

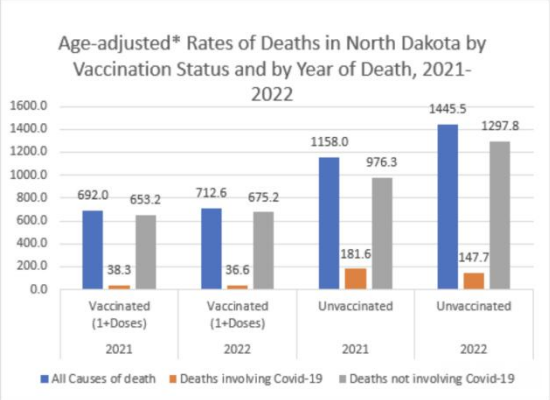
An important task of North Dakota Health and Human Services (HHS) is to monitor the safety of vaccines after they have been released. This project has been described as a hunt for "safety signals," with the process involving three stages: signal detection, signal refinement and signal confirmation.[i]

HHS, with its finite resources, cannot undertake large and complicated studies in aid of post-marketing vaccine safety surveillance.[ii] It therefore is largely dependent in this endeavor on federally-funded primary research. But it is not totally incapable of doing its own primary analytical research because it is already in possession of important data from which safety signals can be gleaned.

4. Death and Vaccination Records

In addition to morbidity, vaccine safety research can also focus on mortality. In this respect, consider that the State maintains its electronic death registration system, so it has ready access to data for all persons who die in the state. It also maintains the North Dakota Immunization Information System for each vaccination given to the individuals. It is therefore possible to merge data from the death records with vaccination data so that, for each person who has died, we will have the individual's vaccination status and information.

HHS has already demonstrated its ability to generate such a data-set. Molly Howell, Immunization Director for the ND HHS, testified at the March 16, 2023 hearing on SB 2384 before the House Human Services Committee. In her written testimony submitted to the committee[iii], Howell presented this graph showing age-adjusted death rates per 100,000 North Dakotans by vaccination status in 2021 and 2022:



*Age-adjusted deaths rates per 100,000 using 2000 U.S. Standard million population (19 Age Groups - Standard Populations - SEER Datasets (cancer.gov)).

This graph could only have been generated from a merged data-set comprised of individual death and vaccination records.

The graph comes from a summary report produced by the ND HHS Health Statistics and Performance Section's Special Projects and Health Analytics Unit. According to Howell, the report was based on records from North Dakota's electronic death records system, Maven (North Dakota's disease surveillance system), and the North Dakota Immunization Information System.[iv]

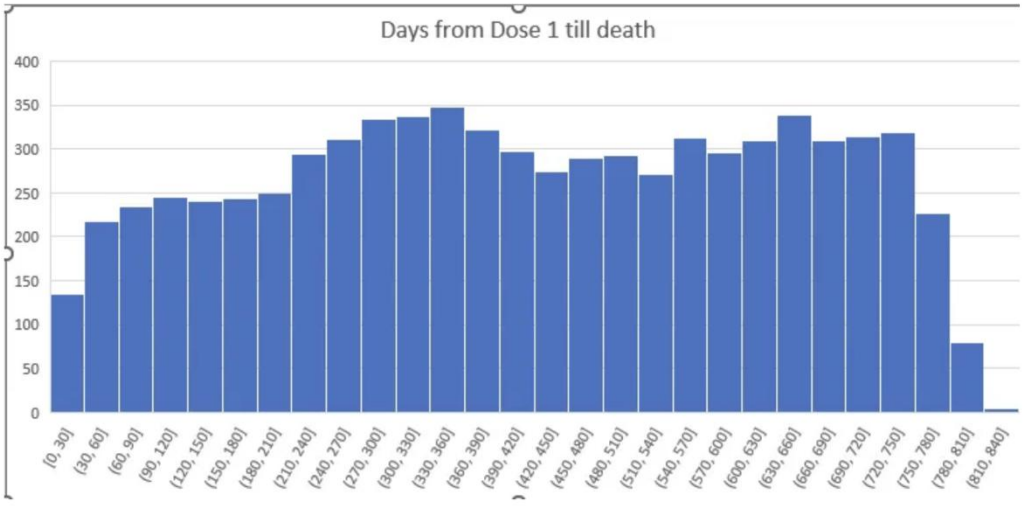
5. Retrospective Cohort Analysis

The researcher doing vaccine safety surveillance has a range of study designs to choose from: cohort, case-control, self-controlled case series, self-controlled risk intervals, and others. Each study design has its advantages and disadvantages.[v]

But the research design most suited to record-level death and vaccination data is the *retrospective cohort study* (also known as time-series cohort analysis).[vi] It is retrospective in that it is looking at vaccinations and deaths that have already occurred. In contrast, a prospective study will start with the individual's exposure to the risk and then observe the individual over time to see if death occurs. In this case, the cohort study will also be *cross-sectional* in that the information regarding the risk factor (vaccination) and the outcome (death) is already present in the data-set and thus is gathered at the same time.

With respect to any vaccine, the cohort in question is comprised of all those individuals who have received a vaccination. The outcome will be death occurring on a given day post-vaccination. This data can be presented in a time-series where the X-axis (horizontal) is time since vaccination measured in days, weeks, or months. The Y-axis (vertical) is the number of deaths occurring on a given day post vaccination. The challenge in the analysis, with to respect signal refinement and signal confirmation, is to determine whether the observed trend is excessive in view of an established baseline.[vii]

Using the COVID vaccines to illustrate: the cohort is the group of individuals who have been exposed to the putative risk by receiving a COVID vaccination. The chronological interval or time period in question is January 1, 2021 through December 31, 2023, the first full three years after the vaccine roll-out. The dated occurrences (deaths) will be arranged temporally by reference to the vaccination date. So for all persons receiving the first dose of the vaccine, for example, the aggregate number of deaths occurring on day 0, 1,2...600... post vaccination can be tallied and displayed in a bar graph. The example graph below shows the aggregate deaths for succeeding 30-day intervals.



With the data available, time-series can be generated by sex, age groups, and other characteristics. Mortality can be expressed in terms of simple counts or in mortality rates such as found in the HHS in-house analysis referred to above.

6. How Does Retrospective Cohort Analysis Handle Common Problems?

A good explanation of common problems facing study designs is found in an article by Sato et al.[viii]

Common problems of study designs include selection bias, misclassification bias (exposure and outcome), and confounding (by indication and time-varying). How well does the proposed cohort analysis handle these problems?

Selection bias generally is related to the way sampling is done. One strategy to ensure that the sample is representative of the general population is to stratify the population according to age, sex, race, etc. However, in this case no sampling is involved because the death and vaccination data-set captures the entire population.

Exposure misclassification bias may occur if the vaccine exposure is not well recorded, leading to a vaccinated person being classified as unvaccinated or vice versa. The reliability of the North Dakota Immunization Information System perhaps can be presumed. One type of case which could introduce bias, however, is the vaccinated out-of-state resident who dies in North Dakota. His vaccination having occurred in another state or country, it would not show up in North Dakota's records. If the vaccine is in fact causing mortality, then this effect will be attenuated by such cases.

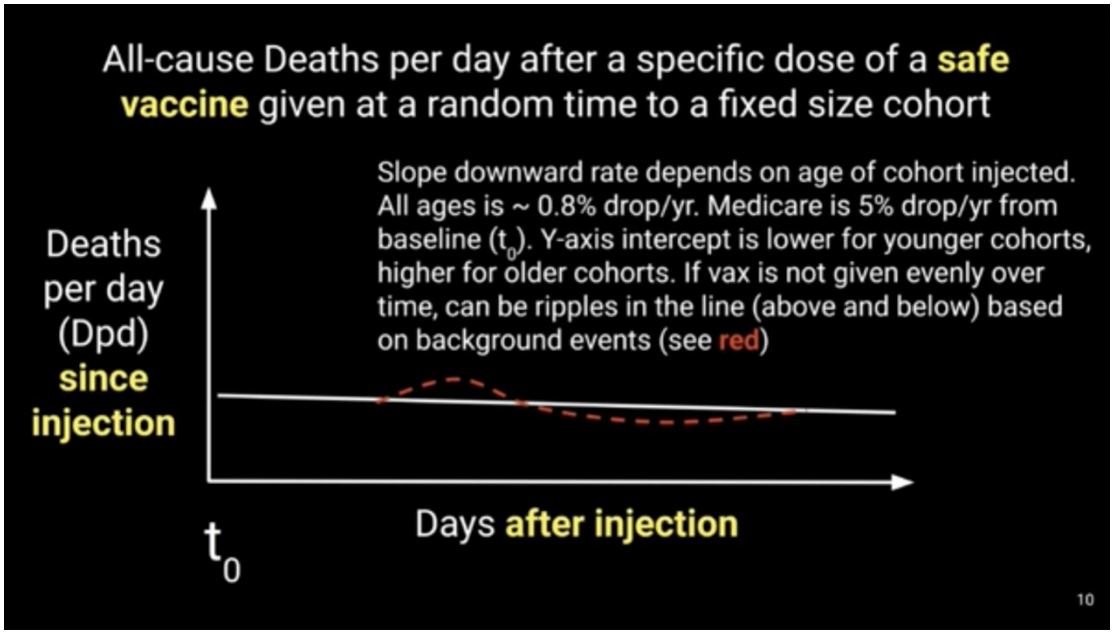
Outcome misclassification bias can arise if vaccine adverse events are misclassified due to faulty diagnoses, miscoding, or other errors. This is not a concern for the cohort analysis of death/vaccination records because the outcome is death, and there is little chance of misclassifying death.

According to Sato et al, other common types of bias are confounding by indication and time-varying confounding, both problematic for cohort analysis. Confounding by indication arises when the probability of being vaccinated is not independent of the probability of the outcome. For example, individuals thought to be at risk for COVID because of age or other comorbidities were prioritized for vaccination. Time-varying confounding occurs when confounders change over time, and it often occurs with time-varying variables such as age, seasonality, and other factors. Both of these sources of bias can be problematic for cohort analysis, but Sato et al report three strategies for mitigating this problem.

The upshot is this type of time-series cohort analysis is another "arrow in the quiver," another tool for vaccine safety monitoring which can play an important role in signal detection, signal refinement and signal confirmation.

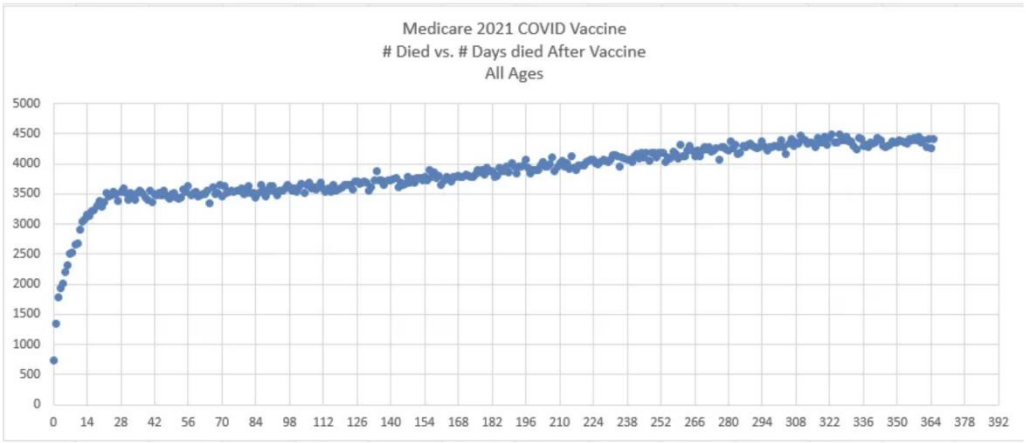
7. How Does Retrospective Cohort Analysis Aid in Safety Signal Detection?

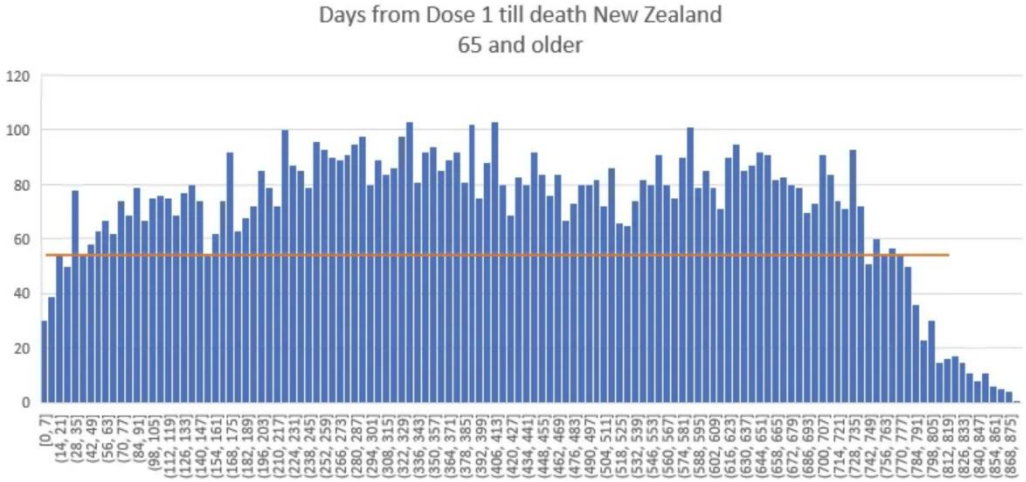
For a safe vaccine, the number of deaths per day for all causes after a specific dose given at random times to a fixed cohort should look like this[ix]:



In simplistic terms, the all-cause mortality line "always slopes downward."

So, there is a safety signal if the all-cause mortality line departs from the expected monotonically declining slope, as in the two sample graphs below:





To be sure, more analysis is required as the researchers work through the process of signal refinement and signal confirmation to a conclusion as to the vaccine's safety, but this presentation should suffice to give an introduction as to how retrospective cohort analysis can aid in signal detection.

8. Proposal for Retrospective Cohort Analysis of COVID Vaccines

Even though the legislation for an interim study did not pass, there is no reason for HHS not to conduct its own retrospective cohort analysis of COVID vaccines as part of its ongoing vaccine safety surveillance effort. The Director should therefore direct the ND HHS Health Statistics and Performance Section's Special Projects and Health Analytics Unit to do the following, with the finer details of the analysis to be determined.

a. Create a Death and Vaccination Data-Set. The data generated should cover the time period starting January 1, 2021 and ending December 31, 2023, the first full three years after the COVID vaccine roll-out. The fields in each record should include an identification number, date of birth, date of death, sex, and race for each individual appearing in the electronic death registration system. Each individual record should also include the following information from the North Dakota Immunization Information System for each COVID vaccination given to the individual: the vaccine type, date of vaccination, vaccine manufacturer, dose number (if applicable), lot number, vaccine provider, and vaccination location.

b. Conduct a Time-Series Cohort Analysis. Many kinds of time-series cohort analyses are possible with this data, but in each variation all-cause mortality will be the dependent variable, whether expressed in terms of death counts or a mortality rate. The independent variables will always include vaccination type (COVID) and time since vaccination, whether expressed in terms of days, weeks, or months. Graphs can be generated by sex, age group (or person-years alive), and so on.

c. Publish the Report.

9. Vaccine Safety Data Transparency Legislation.

In general, the contemplated legislative proposal will require HHS to maintain a death and vaccination database for all vaccines given in this state and make that database available online for public use. To be sure, the personally identifiable information in each record will have to be obfuscated. The legislation will also mandate the publication of time-series cohort analysis for each vaccine on a regular schedule.

The rationale for such legislation is simply the public right to know. Our experience with the COVID vaccines certainly demonstrates the need for such transparency.

Needless to say, the cooperation of HHS in crafting a workable statute will be essential. After all, the burden for implementing this statutory mandate will fall on this agency, and it should have input in the drafting. Based on the experience gained from the COVID "pilot project" proposed in the preceding part 8, HHS will also be able to assess the costs of implementation, develop protocols for protecting personal

identifiable information in the public database, and recommend how to structure the time-series cohort analysis for the vaccines.

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[i] Mesfin YM, Cheng A, Lawrie J, et al Use of routinely collected electronic healthcare data for postlicensure vaccine safety signal detection: a systematic review BMJ Global Health 2019;4:e001065.
[ii] Molly Howell, Immunization Director for the ND HHS, testified at the March 16, 2023 hearing on SB 2384 before the House Human Services Committee. Regarding the feasibility of conducting a full-blown legislative management study, Ms. Howell said: "The North Dakota Department of Health and Human Services (NDHHS) cannot conduct research per federal grants. Formal studies as described in SB2384 would require general funds and additional staffing."
[iii] March 16, 2023 email from Molly A. Howell to House Human Services Committee.
[iv] March 26, 2024 to from Molly A. Howell to Karen M. Rohr.
[v] Lai LY, Arshad F, Areia C, Alshammari TM, Alghoul H, Casajust P, Li X, Dawoud D, Nyberg F, Pratt N, Hripcsak G, Suchard MA, Prieto-Alhambra D, Ryan P, Schuemie MJ. Current Approaches to Vaccine Safety Using Observational Data: A Rationale for the EUMAEUS (Evaluating Use of Methods for Adverse Events Under Surveillance-for Vaccines) Study Design. Front Pharmacol. 2022 Mar 22;13:837632. doi: 10.3389/fphar.2022.837632. PMID: 35392566; PMCID: PMC8980923.
[vi] Stroup and Teutsch, *Statistics in Public Health, Qualitative Approaches to Public Health Problems* (NY Oxford Press, 1998) 97.
[vii] See Lai et al and also *Statistics in Public Health,* p. 110.
[viii] Sato S, Kawazoe Y, Katsuta T, Fukuda H. Comparison design and evaluation power in cohort and self-controlled case series designs for post-authorization vaccine safety studies. PeerJ. 2024 Jan 23;12:e16780. doi: 10.7717/peerj.16780. PMID: 38282861; PMCID: PMC10812582.
[ix] Steve Kirsch Speech at MIT, https://rumble.com/v3yovx4-vsrf-live-104-exclusive-mit-speech-by-steve-kirsch.html