

*BIOS 522: Survival Analysis Methods*

**Activity 8:**

**Cox model extensions**

*This week, we studied several extensions to the model. We learned about stratified Cox models which allow the baseline hazard function to vary across strata. We studied time-dependent covariates and time-varying effects to increase the flexibility of the model.*

Problem 1. COVID-19 Vaccine Effectiveness

The focus of today’s activity is on Lin et al. (2022) *New England Journal of Medicine*, as summarized in Professor Danyu Lin’s presentation to the World Health Organization.

The analyzed data are from the state of North Carolina. Researchers linked data from the state’s COVID-19 vaccination program, state lab’s, and hospitalization surveillance. The purpose of their model was to assess vaccine effectiveness for the prevention of COVID-19, measured as one minus the hazard ratio comparing vaccinated and unvaccinated persons.

Following their notation:

* Let denote the time when an individual is injected with the first dose of a vaccine
* Let denote the vaccine status (0=no vaccine, 1=one dose of Pfizer, 2=two doses of Pfizer, 3=one dose of Moderna, 4=two doses of Moderna, 5=one dose of Janssen)
* Let denote the time when the individual experiences an event of interest (e.g. COVID-19, hospitalization, death)
* Let denote baseline risk factors (i.e., age group, sex, race, ethnicity, geographic region, and county-level vaccination rate)

1. The time origin for the model is the start of the US vaccination rollout (Dec. 11, 2020). Thus, the time scale for the baseline hazard function is calendar time. What is the advantage of using calendar time as the time scale when modeling COVID-19 outcomes?

This model aligns people with respect to calendar time. This is advantageous because epidemic dynamics vary over calendar time. This is best captured by an increased hazard for COVID-19.

*Imagine an individual who is age 50 at baseline. This person is vaccinated with the Janssen vaccine on February 11, 2021.*

|  |  |  |  |
| --- | --- | --- | --- |
| Calendar date | Time since  baseline | Age at baseline | Vaccine status |
| Dec 11, 20 | =0 months | 50 | 0 |
| Jan 11, 21 | =1 month | 50 | 0 |
| Feb 11, 21 | =2 months | 50 | 5 |
| Mar 11, 21 | =3 months | 50 | 5 |

1. Is age at baseline a time-dependent covariate? Why or why not?

No. Age is measured at a fixed point in time (baseline) and thus is considered to be fixed throughout the study.

1. Is vaccine status a time-dependent covariate? Why or why not?

Yes. Individuals are vaccinated over time during the course of the study. People are vaccinated at different times, or not vaccinated at all.

1. Imagine an individual who is age 60 at baseline. This person receives the first dose of the Moderna vaccine on January 11, 2021, and the second dose on February 11, 2021. Fill in their data.

|  |  |  |  |
| --- | --- | --- | --- |
| Calendar date | Time since  baseline | Age at baseline | Vaccine status |
| Dec 11, 20 | =0 months |  |  |
| Jan 11, 21 | =1 month |  |  |
| Feb 11, 21 | =2 months |  |  |
| Mar 11, 21 | =3 months |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| Calendar date | Time since  baseline | Age at baseline | Vaccine status |
| Dec 11, 20 | =0 months | 60 | 0 |
| Jan 11, 21 | =1 month | 60 | 3 |
| Feb 11, 21 | =2 months | 60 | 4 |
| Mar 11, 21 | =3 months | 60 | 4 |

1. Describe the vaccination status over time for an individual who is never vaccinated.

at all times.

*There is interest in assessing if the vaccine effect wanes over time. To support modeling this effect, we add a column for time since first vaccination dose.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Calendar date | Time since  Baseline | Age at baseline | Vaccine status | Time since  first dose |
| Dec 11, 20 | =0 months | 50 | 0 | - |
| Jan 11, 21 | =1 month | 50 | 0 | - |
| Feb 11, 21 | =2 months | 50 | 5 | 0 months |
| Mar 11, 21 | =3 months | 50 | 5 | 1 month |

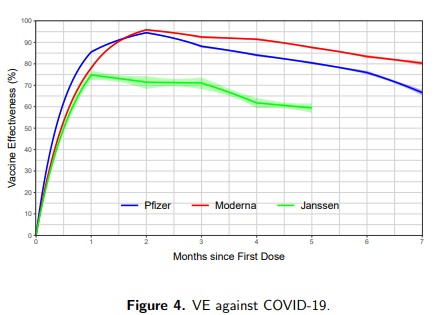
*The effect of vaccine is handled in the model as a time-varying effect, using a model that is piecewise linear within monthly intervals. Vaccine effectiveness over time is estimated from 1 minus the hazard ratio. Vaccine effectiveness is measured separately for each of the three vaccine types (Moderna, Pfizer, and Janssen).*

1. What is the reference group for these hazard ratios?

Unvaccinated individuals.

1. Consider the plot below of vaccine effectiveness (1-hazard ratio) against COVID as a function of months since first dose for each vaccine type. Interpret the findings of the plot.

Vaccine protection initially builds until it peaks, and then it slowly declines. It is highest for moderna and Pfizer.



1. What would this plot look like if the vaccine effect followed a strict proportional hazards model?

VE would be a flat line for each vaccine type.