Web Material

Temporal Confounding in the Test-Negative Design

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Web Appendix 1

TEMPORAL CONFOUNDING IN A CLOSED POPULATION

I. Short vaccine rollout period

We consider a setting where there is some short period at the start of the season when vaccine is still being provided. Vaccination occurs between 0 and t_0. After t_0, no further vaccination occurs. We consider an analysis counting only events occurring after t_0. We denote the cumulative cell count from t_0 to t by $E[\bar{N}^*_{P0}(t)]$, etc.

$$E[\bar{N}^*_{P0}(t)] = n\pi_I\mu_0\big(1 - G(t_0)\big)\big(e^{-\Lambda_I(t_0)} - e^{-\Lambda_I(t)}\big)$$

$$E[\bar{N}^*_{P1}(t)] = n\pi_I\mu_1 G(t_0)(1-\phi)\big(e^{-\Lambda_I(t_0)} - e^{-\Lambda_I(t)}\big)$$

$$E[\bar{N}^*_{N0}(t)] = n\pi_N\mu_0\big(1 - G(t_0)\big)\big(\Lambda_N(t_0) - \Lambda_N(t)\big)$$

$$E[\bar{N}^*_{N1}(t)] = n\pi_N\mu_1 G(t_0)\big(\Lambda_N(t_0) - \Lambda_N(t)\big)$$

The restricted analysis simplifies nicely

$$\frac{E[\bar{N}^*_{P1}(t)]/E[\bar{N}^*_{N1}(t)]}{E[\bar{N}^*_{P0}(t)]/E[\bar{N}^*_{N0}(t)]} = 1 - \phi$$

II. A generic vaccine setting in which there is no temporal confounding

We can solve for a theoretical test positive hazard rate that eliminates temporal confounding. If the test positive hazard rate has cumulative hazard $\Lambda_I(t) = -\log(1 - \lambda^*_I t)$, this will yield an accumulation of test positive cases that is constant over time with rate λ^*_I (although the underlying hazard rate increases to balance ongoing depletion). When this is true and the test negative hazard rate is constant λ_N, there is no temporal confounding.

To achieve a setting with no temporal confounding, the expected value of the four cell counts is the following for some constant λ^*_I:

$$E[\bar{N}_{P0}(t)] = n\pi_I\mu_0\left[\int_{v=0}^{v=t} g(v)\lambda_I^* v dv + \big(1 - G(t)\big)\lambda_I^* t\right]$$

$$E[\bar{N}_{P1}(t)] = n\pi_I\mu_1\int_{v=0}^{v=t} g(v)(1-\phi)(\lambda_I^* t - \lambda_I^* v)dv$$

$$E[\bar{N}_{N0}(t)] = n\pi_N\mu_0\left[\int_{v=0}^{v=t} g(v)\lambda_N v dv + \big(1 - G(t)\big)\lambda_N t\right]$$

$$E[\bar{N}_{N1}(t)] = n\pi_N\mu_1\int_{v=0}^{v=t} g(v)(\lambda_N t - \lambda_N v)dv$$

So then we must set our function $\Lambda_I(t)$ such that:

$$1 - e^{-\Lambda_I(t)} = \lambda_I^* t$$

$$\Lambda_I(t) = -\log(1 - \lambda_I^* t)$$

Web Appendix 2

TEMPORAL CONFOUNDING IN AN OPEN POPULATION

I. Open population, vaccination at time of entry into population, unadjusted odds ratio

Imagine a population that can be subdivided into two cohorts. The first cohort of size n_0 enters at time $t = t_0$. The second cohort of size n_1 enters at time $t = t_1$. Both groups are either immediately vaccinated or not (within each cohort, vax coverage does not change over time). Coverage for the first cohort is ρ_0 and coverage for the second cohort is ρ_1.

Imagine for time $t > t_1$ (population is comprised of both types of cohorts):

$$E[\bar{N}_{P0}(t)] = n_0\pi_I\mu_0(1-\rho_0)\left[1 - e^{-(\Lambda_I(t)-\Lambda_I(t_0))}\right] + n_1\pi_I\mu_0(1-\rho_1)\left[1 - e^{-(\Lambda_I(t)-\Lambda_I(t_1))}\right]$$

$$E[\bar{N}_{P1}(t)] = n_0\pi_I\mu_1\rho_0(1-\phi)\left[1 - e^{-(\Lambda_I(t)-\Lambda_I(t_0))}\right] + n_1\pi_I\mu_1\rho_1(1-\phi)\left[1 - e^{-(\Lambda_I(t)-\Lambda_I(t_1))}\right]$$

$$E[\bar{N}_{N0}(t)] = n_0\pi_N\mu_0(1-\rho_0)\left(\Lambda_N(t) - \Lambda_N(t_0)\right) + n_1\pi_N\mu_0(1-\rho_1)\left(\Lambda_N(t) - \Lambda_N(t_1)\right)$$

$$E[\bar{N}_{N1}(t)] = n_0\pi_N\mu_1\rho_0\left(\Lambda_N(t) - \Lambda_N(t_0)\right) + n_1\pi_N\mu_1\rho_1\left(\Lambda_N(t) - \Lambda_N(t_1)\right)$$

Where $\rho_0 = \rho_1$, the unadjusted test negative design odds ratio simplifies to ϕ. Where $\rho_0 \neq \rho_1$, this will not simplify. This logic extends to more than two cohorts.

Adjusting for calendar time does not eliminate this bias.

$$E[d\bar{N}_{P0}(t)] = n_0(1-\rho_0)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_0))}dt + n_1(1-\rho_1)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_1))}dt$$

$$E[d\bar{N}_{P1}(t)] = n_0\rho_0(1-\phi)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_0))}dt + n_1\rho_1(1-\phi)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_1))}dt$$

$$E[d\bar{N}_{N0}(t)] = n_0(1-\rho_0)\lambda_N(t)dt + n_1(1-\rho_1)\lambda_N(t)dt$$

$$E[d\bar{N}_{N1}(t)] = n_0\rho_0\lambda_N(t)dt + n_1\rho_1\lambda_N(t)dt$$

The time-adjusted odds ratio has expected value:

$$E[OR_{dt}(t)] = \frac{(1-\phi)\left[n_0\rho_0 e^{-(\Lambda_I(t_1)-\Lambda_I(t_0))} + n_1\rho_1\right]/(n_0\rho_0 + n_1\rho_1)}{\left[n_0(1-\rho_0)e^{-(\Lambda_I(t_1)-\Lambda_I(t_0))} + n_1(1-\rho_1)\right]/[n_0(1-\rho_0) + n_1(1-\rho_1)]} \neq (1-\phi)$$

Instead, it is necessary to adjust for cohort. If the population is analyzed separately by cohort, we know from earlier results that this is unbiased within cohorts. This logic extends to more than two cohorts.

II. Open population, vaccination over time but at same rate across cohorts

Consider two cohorts, as in the earlier setting in (B.1). Vaccine is provided over time in each cohort. As vaccine status varies over time, we know that it is necessary to adjust for time. The time-adjusted expected cell counts are:

$$E[d\bar{N}_{P0}(t)] = n_0\pi_I\mu_0\big(1-G_0(t)\big)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_0))}dt + n_1\pi_I\mu_0(1-G_1(t))\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_1))}dt$$

$$E[d\bar{N}_{P1}(t)] = n_0\pi_I\mu_1G_0(t)(1-\phi)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_0))}dt + n_1\pi_I\mu_1G_1(t)(1-\phi)\lambda_I(t)e^{-(\Lambda_I(t)-\Lambda_I(t_1))}dt$$

$$E[d\bar{N}_{N0}(t)] = n_0\pi_N\mu_0\big(1-G_0(t)\big)\lambda_N(t)dt + n_1\pi_N\mu_0(1-G_1(t))\lambda_N(t)dt$$

$$E[d\bar{N}_{N1}(t)] = n_0\pi_N\mu_1G_1(t)\lambda_N(t)dt + n_0\pi_N\mu_1G_1(t)\lambda_N(t)dt$$

In the setting where coverage increases in the same pattern across both cohorts, i.e., where $G_0(t) = G_1(t) \equiv G(t)$, the time-adjusted odds ratio has expected value:

$$E[OR_{dt}(t)] = 1-\phi$$

This logic extends to more than two cohorts.