

## Can we detect treatment effect waning from time-to-event data?

Eni Musta (University of Amsterdam)

Does a vaccine lose its protective power over time? This question matters for public health decisions — like when to recommend booster doses — but answering it turns out to be harder than one might expect. In this talk, we show that standard methods for detecting treatment effect waning from clinical trial data can be misleading. This holds not only for the conventional hazard ratio, which is known to suffer from selection bias, but also for recently proposed causal alternatives, including the "challenge effect" framework based on hypothetical controlled exposure trials. It can for example happen that these estimands suggest waning of treatment effect for both subpopulations but anti-waning for the combined population and vice versa. This phenomenon, which resembles Simpson's paradox and leads to a decision-theoretic contradiction, in this setting occurs even when using properly causal estimands. Moreover, without untestable modelling assumptions, the same observed data can be consistent with two opposite realities: one where the treatment becomes more effective over time for all subpopulations and another where it wanes for all subpopulations. We discuss what assumptions might resolve this paradox and explore some alternative approaches.