**Time-to-event case-control designs: An efficacious tool for cohort studies on nosocomial infections when resources are limited**

Jan Feifel, Martin Schumacher, Jan Beyersmann, Jesus Rodriguez-Baño

**Facts & Figures**

- **Start date**: 01/03/2015
- **End date**: 28/02/2020
- **Contributions**
  - IMI funding: 23,871,500 €
  - EFPIA in kind: 59,833,500 €
  - Other: 1,408,336 €
- **Total Cost**: 85,113,366 €
- **Project website**: www.combacte.com
- **Social media**: twitter.com/combacte

**Challenge**

- Antimicrobial resistance (AMR) is threat to global health, but currently AMR is rare in parts of Europe
- Challenges for researchers investigating incidence and effect of rare exposures (AMR) are manifold:
  - Randomized clinical trials are problematic; microbiology confirmation is required prior to recruitment resulting in low recruitment rates
  - Matching with control patients with carbapenem-susceptible Enterobacteriaceae (CSE) or non-infected admitted patients (ADM)
  - Matched by centre, type of infection, hospital service and acquisition (nosocomial/community)
  - Batch effect in microbiological analysis available
  - Time-to-event methods required for censoring
  - EURECA (European prospective cohort study on Enterobacteriaceae showing Resistance to Carbapenems) is COMBACTE CARE study in 50 sites, 11 countries (Gutierrez-Gutierrez et al. BMJ Open 2017;7:e015365)
  - EURECA aims to assess mortality and length of stay of patients with target infections caused by carbapenem-resistant Enterobacteriaceae (CRE)

**Approach & Methodology**

**Method 1: Nested case-control design (NCC)**

- Cox model \( a(t|Z_i(t)) = \alpha_i(t) \exp(b^T Z_i(t)) \)
  - 0: Admission
  - 1: CRE
- NCC is established method to use limited resources efficiently (CRE infection is rare)
- NCC successfully applied in EURECA study to identify risk factors for CRE infection
- Sampling: For each CRE patient, randomly sample at time of sample verification:
  - one CSE patient, and
  - three ADM patients
- Weighted, stratified analysis takes over the role of a full cohort analysis

**Method 2: Nested exposure case-control design (NECC)**

- Novel methodological extension of NCC funded by DFG
- Motivated by EURECA study to investigate effect of rare time-dependent exposure on subsequent event
- Identify predictors for negative outcomes caused by CRE
- **Sampling at outcome time** but dependent on the previous exposure status

**Results**

- **NECC methodology validated** by application to SIR3 (Spread of nosocomial Infections and Resistant pathogens cohort study) at Charité University Hospital, Berlin, Germany
- SIR3 aims to investigate effect of nosocomial pneumonia (time-dependent) on length of hospital stay (discharge alive or death)
- Study recruited 1,313 patients admitted to intensive care unit
- 8% acquire nosocomial pneumonia, i.e. rare exposure but common outcome event (98%) similar to EURECA
- To validate NECC, bootstrap simulation undertaken to compare NECC to full cohort Cox regression

**Value of IMI collaboration**

- Establishes unprecedented partnership between industry, academia and biotech organizations
- Helps to ensure the success of highly innovative studies (EURECA) and methodology (NECC)
- Enables collaboration between normally disjointed research fields (e.g. clinical infectious diseases and statistics)

**Impact & take home message**

- NECC addresses censoring appropriately, avoids time-dependent bias and performs very well in baseline covariates estimation
- NECC competitively analyses the effect of time-dependent exposure with reduced resources (individuals, determined covariates) to a full cohort analysis
- Procedures applicable for future studies in AMR and other areas of scientific and medical research
- More powerful NECC designs (e.g. history-dependent) possible

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